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# ON CIGARETTE SMOKING, BRONCHIAL CARCINOMA AND CILIARY ACTION*

## I. Smoking Habits and Measurement of Smoke Intake

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STATISTICAL studies have shown a fairly definite association between cigarette smoking and carcinoma of the bronchial tree,[1-11] as well as other effects on the body.[12,13] Some do not accept this association as one of cause and effect. Apparently there are other possible explanations. The validity of the methods of gathering the statistics involved has also come into question.[14] Hoping to add some useful points of information on the dosage of smoke intake and the disposition of smoke in the respiratory tract, I undertook the studies reported in this and subsequent articles.

Tar is a prominent ingredient of smoke,‡ and it is this mixture of substances with which these studies are concerned. It has been known for many years that application of tar to the skin would produce carcinoma. The relation between the tars of coal smoke and carcinoma of the scrotum in chimney sweeps was established more than a hundred years ago.[19] Carcinoma of the skin of animals was produced experimentally by means of tars in 1915,[20] and the experiment has been repeated since then by others. Roffo,[21] Lü[22,23] and Graham,[1] using tar from cigarettes, have also produced carcinoma of the skin. From such experiments, the general impression has been gained and expressed that it is necessary to apply a certain minimal dose of tar over an extended period to produce carcinoma. In mice, the time necessary is between a third and a half of the lifetime of the mouse. If cigarette tar causes bronchogenic carcinoma, it is thought that a like proportion of the life of man is necessary to produce bronchogenic carcinoma from cigarette tar.[1] However, many problems are raised by this concept.

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‡Analysis of the smoke for specific, recognized toxic substances has been made by Bradford et al.,[15,16] Wolman,[17] Derr et al.[18] and others.

### PROBLEMS INVOLVED

#### Light Smokers

Since the percentage of heavy smokers in whom carcinoma develops is small, one would suppose that even heavy smokers must be taking only, or not much more than, the minimum of carcinogenic substance needed to produce a carcinoma, and one would expect that light smokers would never get it. Light smokers do get it, although the incidence is less than that among heavy smokers.

#### Incongruities in Graphs

In some of the graphs published in the study conducted by the American Cancer Society and reported by Hammond,[5-9] there seems to be an incongruity between the effects of one package a day and those of a half a package or less. It appears, from some of these graphs, that at certain ages a fraction of a package is more likely to cause disease than a full one. If such graphs reflect the true comparative dosage of smoke, this would, in my opinion, invalidate the concept that the disease is caused by the cigarettes. The measure of smoke intake ordinarily used is the number of packages or fractions of packages that the subject states he smokes (¼ and ½ package, light; ¾ package, medium; 1 package, fairly heavy; over 1½ packages, chain smoker).

Perhaps, however, the smoker's statement of how many packages he smokes is not a valid measure of smoke intake. On the face of it, one would not think so. Some would minimize and others would exaggerate, and most would probably be depending upon uncertain memory alone. The whole problem would be clarified if the amount of smoke that smokers really take could be accurately ascertained. Failing this, it would even be of value if one could find a possible explanation for the statistical incongruities between the effects of heavy and light smoking.

### Relevance of Skin Experiments to Bronchial Tree

Some believe that the skin experiments cannot be related to smoking because application of concentrated tar to one area of skin is so different from the gentle, diffuse flow of smoke over the large areas of the bronchial tree that it has no relevance.

## Studies of Smoking Habits

Extensive and careful observations on cigarette-smoking habits served as a background to the projected studies. These observations extended over a

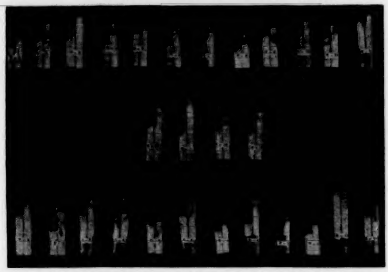

FIGURE 1. *Photograph of 28 Pairs of Partially Burned Cigarettes, Each Pair Coming from the Same Package. The shorter butt of each cigarette is the one left by the smoker, and the longer one the control. The difference between the two is the length burned into the mouth by the smoker.*

period of many weeks and resulted in a number of tables containing a great many figures. Such studies have been made before by others,[15,24-26] and, in a vague, general way, smoking habits are familiar to all. Nevertheless, a brief review of the salient facts with specific figures will be of advantage here. The subjects used in these studies were doctors, nurses and a few visitors in the hospital dining room during lunch and coffee hour. Data were gathered when the subjects were not aware of being observed.

### Length of Butt

The butts of cigarettes left by smokers were examined (Fig. 1 and third column of Table 1), and some were measured. This gave only information as to how much of the cigarette was burned — not how much was burned into the mouth. The butts varied from 23 to 69 mm. and averaged 36.25 mm. in length.

### Number of Puffs per Cigarette

For a single cigarette, the number of puffs or aspirations were counted and averaged in a group of 27 subjects. These varied from 2 to 22, with an average of 9.9. All puffs were not of uniform length, even in 1 subject. Some smokers puff long, and others very briefly.

### Duration of Puff

In 18 smokers the duration of 103 puffs was timed with a stopwatch. It varied from five-tenths second to four seconds and averaged two seconds.

TABLE 1. *Measured Amount of Smoke Taken into the Mouth by Each of 28 Subjects Smoking a Cigarette.**

| Subject No. | Time Not Smoked* | | Length of Smoker's Butt | Length of Control Butt | Amount of Cigarette Burned Into Mouth† |
|---|---|---|---|---|---|
| | *min.* | *sec.* | *mm.* | *mm.* | *mm.* |
| Men: | | | | | |
| 1 | 5 | 46 | 36.5 | 63.0 | 14.5 |
| 2 | 6 | 14 | 30.0 | 48.0 | 18.0 |
| 3 | 7 | — | 45.0 | 59.0 | 14.0 |
| 4 | 9 | 43 | 39.0 | 44.0 | 5.0 |
| 5 | 10 | 30 | 32.0 | 34.5 | 2.5-3.0 |
| 6 | 7 | — | 42.0 | 63.0 | 21.0 |
| 7 | 10 | 13 | 26.0 | 34.0 | 8.0 |
| 8 | 7 | 17 | 38.0 | 58.0 | 20.0 |
| 9 | 12 | 9¼ | 26.0 | 40.5 | 14.5 |
| 10 | 10 | 17 | 25.0 | 32.0 | 7.0 |
| 11 | 3 | 51 | 69.0 | 72.0 | 3.0 |
| 12 | 6 | 22 | 51.0 | 64.5 | 13.5 |
| Average | | | | | 11.7 |
| Women: | | | | | |
| 1 | 5 | 31 | 40.0 | 47.0 | 7.0 |
| 2 | 9 | 11 | 36.0 | 47.0 | 11.0 |
| 3 | 3 | 22 | 38.0 | 56.0 | 18.0 |
| 4 | 9 | 42 | 28.0 | 46.0 | 18.0 |
| 5 | 5 | 43 | 37.0 | 44.0 | 7.0 |
| 6 | 8 | 44 | 23.0 | 36.0 | 13.0 |
| 7 | 6 | 8 | 24.5 | 45.0 | 20.5 |
| 8 | 10 | 36 | 27.0 | 35.0 | 8.0 |
| 9 | 7 | 39 | 33.5 | 41.0 | 7.5 |
| 10 | 9 | 55 | 39.0 | 50.0 | 11.0 |
| 11 | 11 | 34 | 32.0 | 45.0 | 13.0 |
| 12 | 6 | 24 | 49.0 | 58.0 | 9.0 |
| 13 | 7 | 38 | 38.0 | 57.5 | 19.5 |
| 14 | 7 | —‡ | 35.0 | 64.0 | 29.0 |
| 15 | 7 | 6 | 39.5 | 46.0 | 6.5 |
| 16 | 9 | 19 | 36.0 | 50.0 | 14.0 |
| Average | | | | | 13.2 |

*Also time control butt burned.

†Figures arrived at by recording on stopwatch number of minutes & seconds during which subject did not smoke from time he lighted cigarette until he extinguished it (2d column). Control cigarette from same package burned in free air for same number of minutes & seconds in each case. Difference in length between butt of control cigarette (4th column) and butt smoker left (3d column) considered to be amount that he burned into his mouth. (Observations made without smoker's knowledge.)

‡Not entirely accurate — subject held cigarette in mouth for seconds without inhaling.

### Cumulative Puff Time

The cumulative puff time for an entire single cigarette was found in 6 subjects to vary from thir-

teen and eight tenths to thirty-five and two-tenths seconds. It was astonishing that so little total time was actually spent in aspirating.

### Duration of Glow

It was not always easy to time each puff accurately because some subjects stopped aspirating before they took the cigarette from the mouth and some did not begin until they had held it for a second or two. Therefore, an attempt was made to measure the duration of glow. This was measured 18 times but was found to be inaccurate because the ash sometimes covered the glow and, again, one could not be

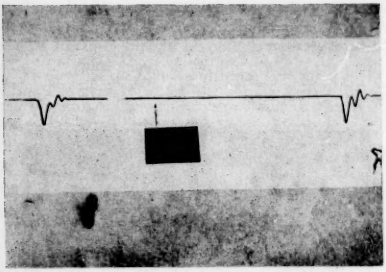

FIGURE 2. *Kymographic Tracing of the Puffs Taken by Subject R.G.*

certain. The duration of glow, as measured, varied from seven tenths to two and two-tenths seconds.

### Pressures Used

The cumulative time of all the puffs used gave a fairly accurate measure of the time during which the

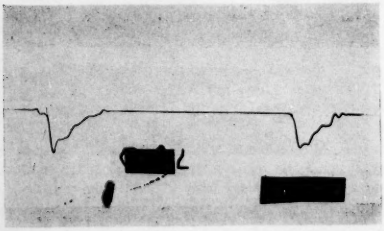

FIGURE 3. *Kymographic Tracing of the Puffs Taken by Subject C.G.L.*

smoker was actually aspirating but was not a measure of smoke intake because some aspirated much more deeply than others. To measure this factor, 12 subjects were taken to the laboratory and asked to smoke a cigarette through a glass Y tube, which acted as a cigarette holder, the other limb of the Y being connected to a water manometer. The results showed a wide variation of pressures used. The average for different smokers varied from 52 to 417 mm. of water — much more than had been anticipated. To carry this phase a little farther, another series of subjects smoked through a Y tube connected to a

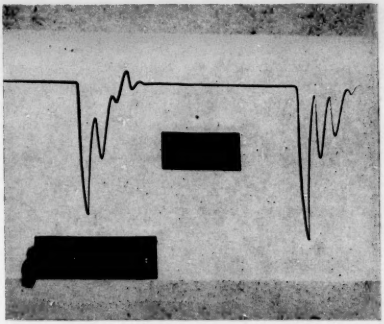

FIGURE 4. *Kymographic Tracing of the Puffs Taken by Subject E.J.S.*
*The pressure is probably exaggerated by "overshoot," in the manometer, as indicated by the oscillations.*

mercury manometer that recorded on a kymograph. More than 80 graphs were made, some of which are shown in Figures 2-6. The shortest and lightest of

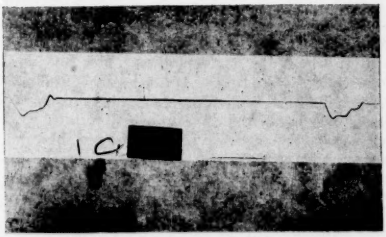

FIGURE 5. *Kymographic Tracing of the Puffs Taken by Subject A.O.S.*

those recorded (translating to water column) were around 70 mm. of water for twenty-five hundredths to three-tenths second. One of the deepest puffs was 204 mm. of water for one and five-tenths seconds. The difference in volume was fifteenfold, and I am sure that this difference is frequently exceeded. It is likely, of course, that these measurements made in the laboratory were materially different from the pressures used in habitual smoking.

### Volume Studies

Volume studies have been made by others,[24] but these are also open to the objection that they cannot

be made without the subject's knowledge and co-operation and may, therefore, differ from volumes used in habitual smoking.

### Measurement of Smoke Intake

None of these studies, singly or in combination, gave information about the amount of smoke taken into the mouth. Entirely too many variables were involved. The problem, in essence, became one of eliminating as many of these variables as possible. Eventually, a simple way was found for determining, with fair approximation, the amount of smoke intake from a single cigarette, expressed in millimeters of cigarette. This was done by means of the rate of burning in free air. The rate at which cigarettes from the same package burn in free air is fairly constant if they are burned about the same time and held in about the same position. The rate varies somewhat between brands, between packs, with moisture content and with atmospheric humidity and the position in which the cigarette is held.

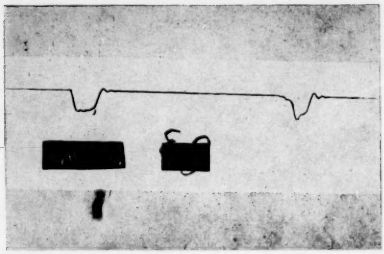

FIGURE 6. *Kymographic Tracing of the Puffs Taken by Subject E.J.*

### Method of Measurement

The simple steps in measuring the amount of smoke taken from a single cigarette, without the knowledge of the smoker, were as follows: observing the smoker from the time he lighted his cigarette until he put it out; timing on a stopwatch the cumulative time between puffs (when the subject was not smoking), during which he simply held the burning cigarette in his fingers or had laid it upon an ash tray to burn; recovering and measuring the butt; obtaining a control cigarette from the same package and burning it in free air for the exact period that the smoker held the one he smoked in his fingers between puffs (the cumulative time showing on the stopwatch); and comparing the length of the remnant of the control with the butt that the smoker left* (the difference was then taken to be the number of millimeters of cigarette that the smoker had burned into his mouth).

Eventually, from many attempts, 28 satisfactory observations were obtained. The variables concerned with atmospheric conditions, moisture content of the cigarette and brand characteristics were all eliminated by means of a control cigarette out of the same package. The variables of smoking habits, such as the number and duration of puffs and the pressure and volume used, were eliminated by the use and measurement of only the time between puffs when the cigarette was burning by itself in free air. The one variable of smoking habits that could not be eliminated was the position in which the cigarette was held by the smoker as it burned between puffs.

### Effect of Position

This point was recently brought up by Proetz,[26] in discussing this method of measuring smoke intake,

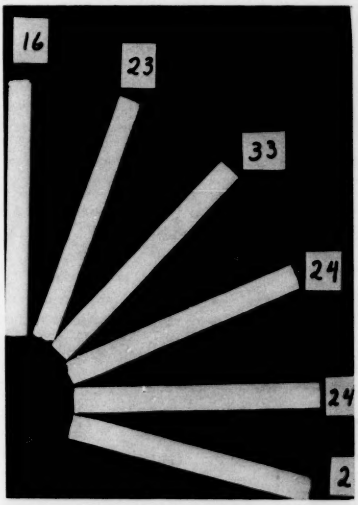


FIGURE 7. *Approximate Positions in Which 122 Smokers, Seated at Tables, Held Their Cigarettes between Puffs, the Figures Indicating the Numbers Observed in Each Position. These smokers were unaware of the study being made.*

when he pointed out that the position in which the smoker holds his cigarette during the time he is not smoking influences the rate of burning. Since I had failed to take the position into account, there was a possibility, therefore, that the control used in the study was inaccurate because, in each case, it was burned in the horizontal position.

Further studies were made to clarify the matter of the control cigarette.

*It was found that some care was necessary in such measurements. If the cigarette had been put out by pressure against a surface, it tended to burn obliquely, even as pressure was made; therefore, the side to be measured was the long side.

*Burning of control cigarette.* Three cigarettes were laid parallel in contact, and all 3 lighted at once, as evenly as possible. One was then placed in a vertical-upright position to burn, 1 horizontally, and the other vertically and inverted. After a given time all 3 were extinguished practically at once. The length of the butts was measured to determine the amount burned. This experiment was repeated eight times, 24 cigarettes being used in all. The total length of cigarette burned in each of the 3 positions proved to be as follows: upright, 455 mm.; horizontal, 444 mm.; and inverted, 527 mm. On an average, the upright burned 2.5 per cent faster, and the inverted 18.7 per cent faster than the horizontal. Therefore, if a smoker among those listed in Table 1 held his cigarette inverted between puffs, the figure representing his intake might be exaggerated significantly. If, on the other hand, he held it upright, the rate of burning would not be greatly different from that of the horizontally burning control, and the figure for his intake would probably be fairly accurate.

*Burning of smokers' cigarettes.* Further observations were made in the same dining room and coffee shop where the first studies were made, the position in which 122 smokers held their cigarettes between puffs being noted. The observations were grouped into six different positions. These positions and the resulting findings are given in Figure 7. The average, as can readily be seen, would lie close to 45° above the horizontal. All these smokers were seated at tables; none were seen to hold cigarettes inverted, and only 2 inclined their cigarettes downward. One of the doctors included in Table 1 was seen on a number of occasions, when standing, to hold his inverted, but when seated at a table, he also held his above the horizontal plane.

A number of smokers were watched while they took several puffs. Most did not seem to hold the cigarette habitually in one position but varied it frequently in the range between the horizontal and upright positions. At one moment, the elbow was resting on the table and the cigarette was near the upright position, and in the next the forearm might be lying on the table and the cigarette inclined anywhere from 10° to 60° above the horizontal. Some smokers changed the cigarette from one hand to the other frequently. Again, the average of the changing positions seemed to be roughly midway between the vertical and horizontal.

To test the difference in rate of burning between 45° and the horizontal position, pairs of cigarettes were burned simultaneously, one in each of these two positions (Fig. 8). They were lighted simultaneously and equally as far as possible. It was not as difficult to light 2 evenly as 3. This may account in part for the more uniform results. The first 3 pairs were of one brand and taken from a package that had been opened several days previously. The next 4 were of another brand and taken from a package freshly opened, and the last 4 from the same package on the following day. All pairs were burned for fifteen minutes and then extinguished practically simultaneously. It was noticed that the cigarettes from the package that had been open for several days burned somewhat faster than those from the freshly opened package. The total length of cigarettes burned in the 11 at 45° was 581 mm. as compared with 586 mm. in the horizontal position. The average per cigarette was 52.8 mm. at 45° and 53.5 mm. in the horizontal, or 0.5 mm. more at the latter position. The average rate per minute was 3.52 mm. as compared with 3.55 mm., or 0.86 per cent faster in the horizontal position than at 45°. The greatest difference in the pairs in length burned was 6 mm. and occurred twice. One was 4 mm., and the difference in the other 8 was less than 2 mm.

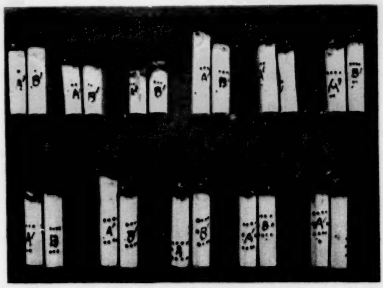

FIGURE 8. *Pairs of Cigarettes, All Burned in Free Air for Fifteen Minutes.*

*A' was above the horizontal position, at an angle of 45°, and B' in a horizontal position. The difference in burning rate between the two positions was insignificant, with two exceptions: the fourth and eighth pairs. (All pairs were not from the same package, and hence the difference in length between some pairs; however, members of each pair came from the same package at the same time.)*

These findings indicate that the average difference in burning rates between the horizontal position and the positions in which smokers hold their cigarettes is not sufficient to be greatly significant. In individual cases the difference could be significant. Therefore, the measurements made must be considered as approximations only, but can be taken as reasonable approximations.

### Photographic Record of Smoke Intake

Figure 1 shows the results of the study on smoke intake photographically. The data are presented in Table 1, in which the men and women are grouped separately. This table, which contains the meat of the study, deserves careful perusal. It is immediately apparent that the amount of cigarette that smokers burn into the mouth from a single cigarette varies

widely (fifth column of Table 1). It was found in these 28 subjects to range from 2.5 to 29 mm. of cigarette, a twelvefold difference.

Also apparent is the fact that the amount taken into the mouth does not parallel at all the number of packs that the subject states he smokes (Table 2). Subject 8 among the women said that she smoked 1 package a day, and Subject 13 half a package, but the former burned only 8 mm. of her cigarette into her mouth whereas the latter took 19.5 mm. Among the men, Subject 11, who smoked 1½ packages a day, burned only 3 mm. into the mouth whereas Subjects 6 and 8, who smoked only 1 package, took 21 and 20 mm. respectively. Subjects 2 and 5 among the men each smoked 2 packages. From the timed and measured cigarettes, the former took 18 mm. into his mouth, and the latter only 2.5 mm.

TABLE 2. *Estimated Amounts of Smoke Taken into the Mouth by 17 Different Smokers in Twenty-four Hours.*

| SUBJECT NO. | SEX | MEASURED INTAKE FROM SINGLE CIGARETTE | NO. OF CIGARETTES SMOKED DAILY* | ESTIMATED TOTAL DAILY INTAKE OF CIGARETTES† |
|---|---|---|---|---|
| | | mm. | | mm. |
| 10 | M | 7.0 | 5 | 35 |
| 15 | F | 6.5 | 10 | 65 |
| 11 | M | 3.0 | 30 | 90 |
| 4 | M | 5.0 | 20 | 100 |
| 5 | M | 2.5-3.0 | 40 | 120 |
| 16 | F | 14.0 | 10 | 140 |
| 8 | F | 8.0 | 20 | 160 |
| 7 | M | 8.0 | 20 | 160 |
| 12 | M | 13.5 | 14 | 189 |
| 13 | F | 19.5 | 10 | 195 |
| 3 | M | 14.0 | 17 | 238 |
| 14 | F | 29.0 | 10 | 290 |
| 1 | M | 14.5 | 20 | 290 |
| 9 | M | 14.5 | 25 | 362 |
| 8 | M | 20.0 | 20 | 400 |
| 6 | M | 21.0 | 20 | 420 |
| 2 | M | 18.0 | 40 | 720 |

*Smoker's statement.

†Calculated by multiplication of measured dose from single cigarette by number that subject stated he smoked, assuming all cigarettes smoked like measured one & smoker's statement correct. For these reasons, estimated dosage cannot be accepted as accurate. However, it gives concept of variation in dosage (here twentyfold) & indicates number of cigarettes smoked not good index of dosage. Subject 5, who smokes 40 cigarettes daily (according to his statement), actually is rather light smoker (120 mm.) as indicated by single measurement. Subject 14, who stated she only smoked half package per day, actually seems to be rather heavy smoker (290 mm.). It is of interest that of 2 who admitted to smoking 40 cigarettes daily, intake of 1 was sixfold that of other (720:120 mm.).

The amount burned per puff varied from 0.7 mm. to 2.7 mm. The women averaged a trifle more per puff than the men, 1.4:1.35 mm. The average number of puffs per cigarette was more for women than men. The ratio was 10:8.1, indicating that the women, in this small group, took more smoke on the average than the men; as far as the intake measurements were concerned, this seemed to be true. The women smoked 13.3 mm. into the mouth, on an average (Table 1), as compared with 11.7 mm. for the men. They averaged 23 per cent more puffs and burned into the mouth 12 per cent more millimeters of cigarette. For figures such as these, this represents a fair correspondence.

## DISCUSSION

This review of smoking habits gave a clear-cut picture of the number, duration and depth of the puffs, with a graphic representation of the results, as well as the amount of cigarette that the smoker left unburned. Among the striking results were the brief period each subject expended inhaling the smoke, from three or four to thirty seconds on a cigarette, and the amount of negative pressure used—up to 400 mm. of water. But none of these observations gave a quantitative measure of the intake of smoke.

There does not seem to be an easy and accurate way of estimating the amount of smoke consumed by a smoker during each twenty-four-hour period. Yet one of the crucial points of interest in the relation of cigarette smoking to bronchogenic carcinoma should be the accurate measurement of the smoke that smokers burn into the mouth. A simple way of determining the amount from a *single* cigarette was devised, as described. This method gives a fair approximation of the length of cigarette that a smoker burns into his mouth from this *one* cigarette. It will not give the *twenty-four-hour intake.* If one could accept the smoker's statement of the number of cigarettes smoked per day, and if one could assume that he smoked the same number of millimeters into his mouth from each of them that he did from the test cigarette, a twenty-four-hour consumption could be calculated. This was done for a group of 17 in Table 2. These results also show great variations. The intake into the mouth for these 17 subjects varied twentyfold—from 35 up to 720 mm. of cigarette. Subject 1 (the fifth from the bottom) stated that he smoked 40 cigarettes (2 packages), and Subject 16 (the sixth from the top) that she smoked only 10, or half a package, a day. It is obvious that the daily intake calculated on this basis does not parallel the stated number of cigarettes smoked daily. It is not to be assumed that this intake figure for twenty-four hours is accurate for the subjects listed in the table, but it does give an indication of the possibilities of and variations in consumption.

It develops, then, from this study that it is possible to measure the length of cigarette that a smoker burns into his mouth. He takes from a single cigarette an amount ranging roughly from 3 to 30 mm., with an average of about 12 or 13 mm.; a low twenty-four-hour consumption is about 100 mm. of cigarette or less, and a high intake may run up to 500 to 700

mm. It would be difficult to determine the twenty-four-hour consumption in any given smoker. To do so would require an actual count of the cigarettes smoked and measurement of at least enough to get a satisfactory average; these cigarettes should be smoked under the varying circumstances of his daily routine and the observations made without his knowledge — a difficult task indeed!

One important result of this study is the indication that incongruities in statistical studies, such as those reported by Hammond for the American Cancer Society, do not necessarily speak against the relation of cigarette smoking to disease but may only indicate that the measure of consumption used is inaccurate. The answer to the question why, since carcinoma develops in a very small percentage of heavy smokers, light smokers ever get it may lie in the definition of a "light smoker." A person who smokes half a package and is classified as a light smoker may still be taking 200 or 300 mm. of cigarette, which would constitute a fairly heavy intake.

It should be pointed out that the amount of smoke taken into the mouth is not necessarily a measure of the dose of toxins taken into the lungs. What the subject does with the smoke after receiving it into his mouth is another story, which will be discussed in a subsequent article.

## Summary and Conclusions

The smoker's statement of the number of cigarettes that he smokes is not a reliable measure of the amount of smoke taken into his mouth. A simple method whereby the amount burned into the mouth from a single cigarette could be determined approximately is described.

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# A CORRELATIVE STUDY OF VALVULAR MORPHOLOGY AND CLINICAL RESULTS IN AORTIC COMMISSUROTOMY*

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THE surgical treatment of rheumatic aortic stenosis depends upon the ability to split commissural fusion by digital or instrumental means. The initial technic[1] required an entrance into the left ventricle through its muscular wall, but more recently the aorta itself has served as the portal to the valve.[2]

The results of the operation reveal significant clinical improvement in many patients with major manifestations of the lesion.[3,4] Furthermore, physiologic data in a small series of patients have shown that striking modifications in pressure gradients across the orifice of the valve are attainable.[5] These encouraging results are tempered by specific cases in which the devolutionary clinical and physiologic patterns are not altered by surgery.[3,4]

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The basic premise of surgery for any stenotic lesion is that clinical improvement is directly dependent upon the surgeon's ability to restore a modicum of function by enlarging the orifice of the valve without causing regurgitation.

Unfortunately, the accessibility of a valve is not a priori evidence that it is susceptible to surgical correction. Indeed, it is entirely possible for technics to be seriously compromised by the morphology of the diseased valve. It is a logical contention, therefore, that the ultimate value of surgery is intimately related to the physical characteristics of the stenotic valve and its response to available surgical methods.

This study has been undertaken to clarify the relation between the morphology of the aortic valve in rheumatic stenosis and the ability to increase the size of the orifice by surgery and the clinical response of the patient. The material has been gathered from a group of patients who have undergone transaortic commissurotomy for aortic stenosis alone or in combination with adynamic aortic regurgitation. The transaortic technic permits direct digital examination of the leaflets before and after definitive operative measures.

TABLE 1. *Duration of Follow-up Study.*

| POSTOPERATIVE PERIOD | NO. OF PATIENTS |
|---|---|
| *mo.* | |
| 3 - 5 | 6 |
| 6 - 8 | 7 |
| 9 - 11 | 6 |
| 12 - 15 | 7 |
| 16 - 25 | 3 |
| Total | 29 |

TABLE 2. *Relation of Palpable Valvular Calcification and Age.*

| CALCIFICATION | NO. OF CASES | MEAN AGE |
|---|---|---|
| | | *yr.* |
| None | 5 | 32.2 |
| Minimal | 4 | 39.0 |
| Moderate | 10 | 43.2 |
| Marked | 21 | 46.6 |

## MATERIAL

The 40 patients considered in this study were operated on during the interval from March, 1953, to January, 1955, and consisted of 34 males and 6 females whose ages range from twenty to sixty years. Twenty-two had pure aortic stenosis, and 18 had an additional element of aortic insufficiency that was considered adynamic.

## METHODS

At operation, the surgeon determined the presence, location and extent of both calcification and thickening of the valve, residual function (mobility) and the type and size of orifice. The last measurement was re-estimated immediately after commissurotomy.

Calcification and thickening were classified as none, minimal, moderate and marked. Function was considered adequate when the leaflets were flexible and mobile, restricted when these features were seriously compromised and fixed when the leaflets were inflexible and immobile.

The clinical manifestations before and after operation were studied independently, with no knowledge of the conditions discovered at the time of operation.

TABLE 3. *Relation between Valvular Mobility, Thickening and Age.*

| MOBILITY | NO. OF CASES | MINIMAL VALVULAR THICKENING | MODERATE VALVULAR THICKENING | MARKED VALVULAR THICKENING | MEAN AGE |
|---|---|---|---|---|---|
| | | NO. OF CASES | NO. OF CASES | NO. OF CASES | |
| | | | | | *yr.* |
| Adequate | 12 | 5 | 7 | — | 41.2 |
| Restricted | 19 | — | 10 | 9 | 44.2 |
| Fixed | 9 | — | 3 | 6 | 43.9 |

The follow-up period extended from three to twenty-five months (Table 1). This material, in more specific detail, forms the basis of a separate report on the therapeutic effectiveness of transaortic commissurotomy.[4] For the purposes of the present correlation the condition of the surviving patients was recorded merely as improved, unchanged and worse. In addition, the causes and circumstances of death, if known, were listed separately.

## RESULTS

### Valvular Morphology

Leaflet calcification was detected in 35, or 87.5 per cent, of the patients. It was marked in 52.5 per cent, moderate in 25 per cent and minimal in 10 per cent. Table 2 indicates the increase in the severity of calcification with the age of the patient.

Significant leaflet thickening independent of calcification was observed in 35, or 87.5 per cent, of the patients. There was little correlation between severity of thickening and age of the patient (Table 3).

The function of the leaflets was impaired significantly in 28, or 70 per cent, of the patients, and in 22.5 per cent the change was extreme. Tables 3 and 4 demonstrate the interrelation of calcification, thickening and restricted or fixed leaflet mobility. From these figures it is apparent that 68.4 per cent of the valves with restricted mobility and 88.8 per

cent of the fixed valves were heavily calcified. Although only 47.3 per cent of the restricted valves were markedly thickened, 66.6 per cent of the fixed group were similarly involved.

Commissural fusion occurred in 38, or 97.4 per cent, of the 39 patients in whom the observation was recorded. Three commissures were fused in 78.9 per cent, and 2 in 21.1 per cent (Table 5).

A bicuspid type of valve was reported in 8, or 20 per cent, of the patients, and, with 1 exception, these were markedly calcified and immobile.

In 16, or 42.1 per cent, of the 38 patients in whom the determination was made the aortic orifice was less than 0.5 sq. cm. before attempts at commissural separation. In 22, or 57.9 per cent, it was estimated as between 0.5 and 0.8 sq. cm. (Table 6).

TABLE 4. *Relation between Valvular Mobility and Palpable Valvular Calcification.*

| Valvular Mobility | No. of Cases | Marked Palpable Calcification | Moderate Palpable Calcification | Minimal Palpable Calcification | No Palpable Calcification |
|---|---|---|---|---|---|
| | | no. of cases | no. of cases | no. of cases | no. of cases |
| Adequate | 12 | — | 5 | 3 | 4 |
| Restricted | 19 | 13 | 5 | — | 1 |
| Fixed | 9 | 8 | — | 1 | — |

TABLE 5. *Success in Commissural Separation in 39 Cases.**

| No. of Fused Commissures | No. of Cases | 3 Commissures Opened at Surgery | 2 Commissures Opened at Surgery | 1 Commissure Opened at Surgery | No Commissure† Opened at Surgery |
|---|---|---|---|---|---|
| 3 | 30 | 4 | 19 | 5 | — |
| 2 | 8 | — | 3 | 5 | — |
| 0 | 1 | — | — | — | 1 |

*Two cases excluded because number of commissures opened not specified.
†One case omitted because amount of fusion not mentioned.

## Postoperative Orifice in Relation to Morphology

Five patients were excluded from this correlation because of inadequate data or the production of dynamic aortic insufficiency at the time of operation. In the latter instance it is clear that the final size of the orifice represents the result of excessive valvular mobilization carried beyond morphologic limitations.

An aortic-valve orifice of 1.6 sq. cm. or greater was arbitrarily accepted as an adequate anatomic result.

Surgery increased the opening to at least 1.6 sq. cm. in 24, or 68.5 per cent, of the patients, to an area between 1.0 and 1.6 sq. cm. in 8, or 22.8 per cent, and to less than 1.0 sq. cm. in 3, or 8.5 per cent. Thus, commissurotomy was successful in establishing an adequate orifice in approximately 7 of every 10 patients of this group (Table 7).

A satisfactory opening was created in each of the 3 patients who had no leaflet calcification, in 10, or 71.4 per cent, of those with minimal to moderate calcification and in 11, or 61.1 per cent, of those with marked calcific deposits. Accordingly, the production of an adequate orifice decreased with the severity of calcification.

A satisfactory orifice was obtained in 3, or 75 per cent, of the cases in which valvular thickening was minimal. On the other hand, an equal result was achieved in only 7, or 53.8 per cent, of the patients with marked thickening. As before, adequate enlargement was inversely related to the degree of thickening.

In brief, an adequate valvular orifice was obtained in approximately 5 of every 10 patients, varying degrees of calcification and thickening notwithstanding.

The anatomic opening was adequate in only 1, or 14.3 per cent, of the patients in whom the leaflets were fixed and in 23, or 82.1 per cent, of those with either restricted or unaltered valvular function.

From these experiences, an immobile leaflet was found to be the most profound single deterrent to the likelihood of an adequate orifice. In the presence of an immobile valve, realization of success is reduced to approximately 1 in every 7 attempts.

An orifice of satisfactory size was obtained in only

TABLE 6. *Relation between Clinical Result and Estimated Size of Orifice before and Immediately after Operation.*

| Clinical Result | No. of Cases | Preoperative Size <0.5 Sq. Cm. | Preoperative Size 0.5 - 0.8 Sq. Cm. | Postoperative Size 0.5 - 1.0 Sq. Cm. | Postoperative Size 1.1 - 1.5 Sq. Cm. | Postoperative Size 1.6 - 2.0 Sq. Cm. | Postoperative Size 2.1 - 2.5 Sq. Cm. |
|---|---|---|---|---|---|---|---|
| | | no. of cases | no. of cases | no. of cases | no. of cases | no. of cases | no. of cases |
| Improved* | 23 | 6 | 17 | — | 4 | 14 | 4 |
| Same | 2 | 1 | 1 | 1 | 1 | — | — |
| Worse† | 4 | 1 | 1 | — | — | 1 | 1‡ |
| Operative deaths | 4 | 4 | — | 2 | — | 1 | 1‡ |
| Late deaths | 7 | 4 | 3 | — | 3 | 4 | — |

*Postoperative size of orifice not recorded in 1 case.
†No accurate data in 2 cases; dynamic aortic insufficiency created in 1 of these.
‡Significant aortic insufficiency created.

1, or 14.3 per cent, of the 7 patients with the combination of heavily calcified, immobile valves in whom the measurement was recorded (Table 8). This represented the most ominous morphologic pattern encountered by the surgeon.

Table 7. *Relation of Immediate Postoperative Orifice Size and Valvular Morphology.**

| Estimated Postoperative Orifice Size | No Valvular Calcification | Minimal Valvular Calcification | Moderate Valvular Calcification | Marked Valvular Calcification | Minimal Valvular Thickening | Moderate Valvular Thickening | Marked Valvular Thickening | Adequate Valvular Mobility | Restricted Valvular Mobility | Fixed Valvular Mobility |
|---|---|---|---|---|---|---|---|---|---|---|
| | | No. of cases | No. of cases | No. of cases | No. of cases | No. of cases | No. of cases | No. of cases | No. of cases | No. of cases |
| *sq. cm.* | | | | | | | | | | |
| 0.5 - 1.0 | — | 1 | — | 2 | — | 1 | 2 | — | — | 3 |
| 1.1 - 1.5 | — | 1 | 2 | 5 | 1 | 3 | 4 | 2 | 3 | 3 |
| 1.6 - 2.0 | 2 | 2 | 7 | 9 | 3 | 13 | 4 | 7 | 12 | 1 |
| 2.1 - 2.5 | 1 | — | 1 | 2 | — | 1 | 3 | 1 | 3 | — |

*Two cases excluded because of inadequate data, and 3 cases because of dynamic aortic insufficiency produced at surgery; all valves had estimated preoperative orifice size of 0.8 sq. cm. or less.

### Postoperative Clinical Status in Relation to Morphology (Tables 9-11)

Four, or 10 per cent, of the patients died at surgery. Twenty-three, or 63.8 per cent, of the remainder were improved, 2, or 5.5 per cent, were unchanged, and 4, or 11.1 per cent, were worse. Seven, or 19.4 per cent, died while under observation after operation. For the purpose of analysis, all patients who were not definitely improved by surgery were considered to have had an adverse result.

Table 8. *Morphologic and Clinical Results in Patients with Fixed Valves.*

| Patient | Calcification | Thickening | Postoperative Orifice | Clinical Result |
|---|---|---|---|---|
| | | | *sq. cm.* | |
| P.S. | Marked | Marked | 1.8 | Late death (subacute bacterial endocarditis) |
| C.D. | Marked | Marked | 1.5 | Late death (subacute bacterial endocarditis) |
| H.M. | Marked | Marked | 1.5 | Improved |
| A.W. | Marked | Marked | 1.5 | Improved |
| A.W. | Marked | Marked | 1.0 | Operative death (hemorrhage) |
| J.H. | Marked | Marked | 1.0 | Operative death (ventricular fibrillation) |
| J.A. | Minimal | Moderate | 0.5 | Unimproved |
| P.B. | Marked | Moderate | — | Operative death (massive infarction) |
| H.P. | Marked | Moderate | No accurate data | Worse |

The response to surgery was not influenced by the presence of marked leaflet calcification per se, since 12, or 52.1 per cent, of those benefited and 9, or 52.9 per cent, of those with an adverse response had that finding.

Similarly, marked leaflet thickening itself did not affect the ultimate clinical status since 9, or 39.1 per cent, of the improved and 5, or 29.4 per cent, of the unimproved groups had this finding. Paradoxically, minimal thickening was encountered in more patients (23.5 per cent) who were not improved than in those who were (only 4.3 per cent).

An immobile valve had a distinct relation to the final clinical outcome since it was present in only 2, or 8.7 per cent, of those who were improved and in 7, or 41.2 per cent, of the patients with an adverse result. Adequately functioning valves were equally distributed in both groups.

The combination of severe leaflet calcification and immobility was present in 2, or 8.7 per cent, of the patients with a satisfactory result and in 6, or 35.3 per cent, of those with an adverse response.

The postoperative orifice was increased to an acceptable area in 18, or 81.8 per cent, of 22 improved patients in whom the measurement was made (Table 6). Excluding the 3 cases in which dynamic insufficiency was produced, an equivalent anatomic result was recorded in only 6, or 35.3 per cent, of the unimproved patients.

## Discussion

An attempt has been made to define the interrelations between valvular morphology, size of orifice and clinical results after aortic commissurotomy. The investigation, therefore, has been limited to data ascertained by the sense of touch during surgery. Although obvious limitations are imposed by this type of inquiry, the information gained suggests that it is both pertinent and useful.

Since the patients in this study revealed marked severity in both structural and functional abnormalities of the aortic valve, the natural conclusion develops that surgery for symptomatic aortic stenosis is generally carried out in the presence of difficult mechanical problems that are discovered alone or in various combinations. In proportion to their severity, they hinder the efficacy of surgical enlargement of the narrowed aortic orifice. The most difficult mor-

phologic manifestation has been the combination of marked calcification and leaflet immobility.

This analysis suggests that 20 per cent of the patients with severe manifestations of aortic stenosis possess heavily calcified, fixed valves that negate the possibility of materially increasing the size of the orifice. When to these are added the number of patients whose relatively advanced valvular disease also proves insurmountable, the risk of surgical failure increases to approximately 30 per cent.

These failures do not obscure the record of success when the leaflets, although thickened or calcified, retain some flexibility. In short, whereas the likelihood of a successful commissurotomy decreases in proportion to the severity of the structural abnormalities, it is not eliminated until all vestiges of normal leaflet function are destroyed. Occasionally, this pattern of achievement is altered inexplicably in that the size of the opening may not be increased satisfactorily when the morphology is favorable. On the other hand, the valve may be opened successfully in spite of advanced morphologic changes. This is probably related to local structural idiosyncrasies that permit satisfactory commissural separation in an otherwise "frozen" valve.

A concerted direct study of structural and functional characteristics by means of the technic of McMillan et al.[6] may eventually clarify the apparent inconsistencies. Nevertheless, the relation between morphology and the attainment of an adequate orifice is such as to discourage the intervention when the unfavorable conditions are recognized and to warrant it under all other circumstances.

The most disturbing problem is the inability to predict, before actual operation, the existence of the morphologic type that precludes a satisfactory result. A review of the clinical material fails to define patterns that are associated with specific structural findings. Very limited aid is granted by the ordinary methods of study. X-ray and fluoroscopic examinations may identify marked calcification, but do not specify the 40 per cent of the patients with this finding who also possess immobile leaflets.

This problem deserves emphasis because the penalty of surgical intervention when the valve is both calcified and immobile extends beyond mere technical failure. In these patients the likelihood of death at operation is considerable. Indeed, in the present series the acute mortality, with 1 exception, was limited to this group. In all 3 patients who died on the operating table, the fatal outcome was precipitated by either an uncontrollable splitting of the rocklike tissue, resulting in lethal insufficiency, or ventricular fibrillation and hemorrhage after repeated attempts to open the valve.

A marked diminution in the area of the aortic orifice characterized all the operative findings before commissurotomy. Analysis of the patients who survived surgery reveals a distinct correlation between clinical improvement and success in enlarging the stenotic aortic valve.

TABLE 9. *Relations of Valvular Morphology and Clinical Result.*

| CLINICAL STATUS | NO VALVULAR CALCIFICATION | MINIMAL VALVULAR CALCIFICATION | MODERATE VALVULAR CALCIFICATION | MARKED VALVULAR CALCIFICATION | MINIMAL VALVULAR THICKENING | MODERATE VALVULAR THICKENING | MARKED VALVULAR THICKENING | ADEQUATE VALVULAR MOBILITY | RESTRICTED VALVULAR MOBILITY | FIXED VALVE |
|---|---|---|---|---|---|---|---|---|---|---|
| | NO. OF CASES | NO. OF CASES | NO. OF CASES | NO. OF CASES | NO. OF CASES | NO. OF CASES | NO. OF CASES | NO. OF CASES | NO. OF CASES | NO. OF CASES |
| Improved | 3 | 2 | 6 | 12 | 1 | 13 | 9 | 7 | 14 | 2 |
| Same | — | 1 | 1 | — | 1 | 1 | — | 1 | — | 1 |
| Worse | 2 | — | — | 2 | 2 | 1 | 1 | 2 | 1 | 1 |
| Operative deaths | — | — | — | 4 | — | 2 | 2 | — | 1 | 3 |
| Late deaths | — | 1 | 3 | 3 | 1 | 4 | 2 | 2 | 3 | 2 |

TABLE 10. *Operative Deaths.*

| CAUSE OF DEATH | NO. OF PATIENTS | TIME RELATION | VALVULAR MORPHOLOGY | | | ESTIMATED ORIFICE SIZE | |
|---|---|---|---|---|---|---|---|
| | | | CALCIFICATION | THICKENING | MOBILITY | BEFORE COMMISSUROTOMY | AFTER COMMISSUROTOMY |
| | | | | | | *sq. cm.* | *sq. cm.* |
| Laceration of aortic leaflet | 1 | Immediate | Marked | Marked | Fixed | 0.5 | 2.1* |
| Ventricular fibrillation | 1 | Immediate | Marked | Marked | Fixed | 0.5 | 1.0 |
| Hemorrhage | 1 | Immediate | Marked | Marked | Fixed | 0.5 | 1.0 |
| Cerebral embolism | 1 | 6 hr. | Marked | Moderate | Restricted | 0.5 | 1.8 |

*Infarction.

A relatively arbitrary size of orifice was chosen as the minimal satisfactory aortic-valve area. Thus, no attempt has been made to define the critical size required for alleviation of the clinical manifestations of the disease. Indeed, it would be a gross oversimplification to speak of a basic area requirement unless other parameters such as flow, cardiac rate and myocardial factors are considered. However, it is pertinent to restate the observation that significant benefit accrues in patients with symptomatic aortic stenosis when the area of orifice is increased to at least twice its preoperative size, provided insufficiency is not produced.

Certain inconsistencies are apparent in the cases in which the clinical result did not correlate with the surgical achievement. An example is the occurrence of sudden death in a patient who obtained a satisfactory valve opening after surgery.

Furthermore, it is quite clear that the size of the orifice achieved by surgery is no protection against the future development of subacute bacterial endocarditis. This complication appears much more likely when the leaflets are severely calcified and sharply limited in mobility regardless of the adequacy of the opening.

The greater likelihood of achieving an adequate aortic-valve area and subsequent clinical improvement under less imposing morphologic conditions is a logical corollary to the basic concept of surgery for aortic stenosis. Although it is impossible at present to define and predict the exact structural point at which the hope for surgical reclamation must be viewed as unlikely, it is apparent that this is a pressing necessity. Furthermore, it is probable that irreversible morphologic patterns frequently accompany the far-advanced symptomatology of the prohibitive surgical risks. These considerations suggest the logic of earlier operative intervention.

TABLE 11. *Causes of Death and Anatomic Findings.*

| CAUSE OF DEATH | ORGANISM | TIME AFTER SURGERY | VALVULAR MORPHOLOGY | | | ESTIMATED ORIFICE SIZE | |
|---|---|---|---|---|---|---|---|
| | | | CALCIFICATION | THICKENING | MOBILITY | BEFORE COMMISSUROTOMY | AFTER COMMISSUROTOMY |
| | | *mo.* | | | | *sq. cm.* | *sq. cm.* |
| Subacute bacterial endocarditis | Friedländer's bacillus | 2.0 | Marked | Moderate | Restricted | 0.5 | 1.5 |
| Subacute bacterial endocarditis | Coagulase-negative staphylococcus | 3.0 | Marked | Marked | Fixed | 0.5 | 1.5 |
| Subacute bacterial endocarditis | Coagulase-negative staphylococcus | 14.0 | Moderate | Moderate | Restricted | 0.5 | 2.0 |
| Subacute bacterial endocarditis | Coagulase-negative staphylococcus | 2.0 | Marked | Marked | Fixed | 0.5 | 1.8 |
| Unknown* | — | 5.0 | Moderate | Moderate | Adequate | 0.5 | 1.8 |
| Unknown* | — | 5.0 | Minimal | Minimal | Adequate | 0.5 | 2.0 |
| Unknown* | — | 2.5 | Moderate | Moderate | Restricted | 0.5 | 1.5 |

*Sudden death.

## SUMMARY AND CONCLUSIONS

A rather consistent correlation between the postoperative size of the aortic-valve orifice and clinical result has been demonstrated.

A grossly reciprocal relation is demonstrable between severity of valvular disease and success in attaining an adequate aortic-valve orifice.

Adequate orifice enlargement and subsequent clinical improvement frequently occur despite marked calcification and significant thickening, *provided* that some measure of residual valvular mobility remains.

Postoperative orifice size is influenced chiefly by residual valvular mobility, which, in turn, is limited by degree of calcification and thickening. Presence of the last two elements does not necessarily preclude some measure of residual mobility.

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# TESTICULAR FEMINIZATION IN A MALE PSEUDOHERMAPHRODITE

## Report of a Case

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THERE are both male and female types of pseudohermaphrodites, the designating factors being the gonads. Thus, in male pseudohermaphrodites the gonads are testes, whereas the external genitalia are female. Conversely, in female pseudohermaphrodites the gonads are ovaries, but male tendencies are seen in the organs of reproduction. Because of all this, investigators are agreed that, regardless of the body appearance, the sex of the patient is determined by the type of sex glands that are present.

The incidence of pseudohermaphroditism has been reported by Young[1] to be as high as 1 in 1000 persons. In most of these cases the sex is obvious, and the only abnormality is a slight alteration of the genitalia. A few cases are regarded as constituting a subgroup of male pseudohermaphrodites; in this group the patients are normal-appearing females whose gonads are testes. We prefer to call this anomaly the testicular-feminizing syndrome in male pseudohermaphrodites.

Morris[2] recently reviewed the literature and made a résumé of all the cases of this subtype of male pseudohermaphrodites. He described the syndrome found in normal-appearing women whose gonads are testes rather than ovaries. It is interesting that the syndrome has strong familial tendencies, as demonstrated by the number of cases reported in sisters. One of the most interesting of these, presented by Ward-McQuaid and Lennon,[3] concerns 2 sisters who were operated on for inguinal hernia; it was found that the sac contained male gonads and no female sex organs.

The case reported below is added to the literature because no previous case appears to have been studied as completely as this case. The patient was one of 3 sisters, all of whom presented abnormalities of the reproductive system.

### CASE REPORT

A.R., a 17-year-old girl, was admitted to the surgical service on August 20, 1954, because of right-lower-quadrant pain of 3 weeks' duration. She had noticed similar episodes during the preceding 18 months; nausea and vomiting occasionally occurred in association with these pains.

Physical examination revealed a tall, thin, quiet girl (Fig. 1) in no apparent distress. The head and neck were not remarkable. Examination of the chest disclosed a normal heart and lungs; the breasts were small and rounded, and no secretion from the nipples was obtained on pressure. The abdomen was within normal limits except for minimal tenderness in the right lower quadrant. No lymph nodes were palpable in the neck, axillary or inguinal regions. There was practically no axillary hair. Neurologic examination was completely within normal limits.

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The temperature was 99.4°F., the pulse 120, and the respirations 16. The blood pressure was 100/70.

Pelvic examination revealed only a minimal amount of pubic hair; the labia majora and minora were normal, as was the clitoris. The introitus barely admitted the examiner's index finger; the vagina was a blind pouch, 10 cm. in length. No uterine structure was palpable.

Examination of the blood disclosed a red-cell count of

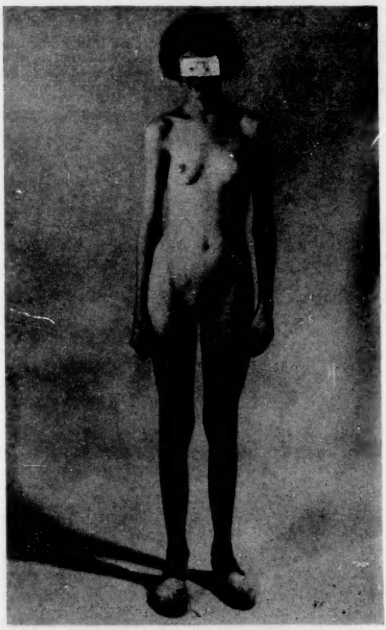

FIGURE 1. *Appearance of A.R.*

4,300,000, with a hemoglobin of 13.4 gm. per 100 ml., and a white-cell count of 8000, with 72 per cent neutrophils, 6 per cent band forms, 18 per cent lymphocytes, 3 per cent monocytes and 1 per cent eosinophils. Urinalysis was within normal limits. The stools disclosed no ova or parasites. The blood serologic test was negative. A circulatory eosinophil count showed 140 eosinophils per cubic millimeter. A test with 1st-strength P.P.D. was positive.

A chest film disclosed a normal cardiac silhouette; the apex showed scattered flecks of calcium. Roentgenograms of the upper and lower gastrointestinal tract and genitourinary system were normal.

Anthropologic measurements were as follows: height, 170 cm.; weight, 47.2 kg. (104 pounds); fingertip to fingertip, 175 cm.; top of head to buttocks, 94 cm.; and lower extremities, 76 cm. (Fig. 1).

Urinary pituitary gonadotrophins, 17-ketosteroids and estrogenic level were within normal limits (Table 1).

An exploratory laparotomy was done on August 25, 1954. Findings at operation were reported as follows:

"On opening the abdomen it was found that there was a complete absence of the uterus and cervix . . . The so-called Fallopian tube on the left was much more immature than the one on the right. The gonad on the right was of normal size, but on taking a biopsy appeared not to have normal ovarian tissue, and resembled more definitely a male gonad. The left ovary was much smaller. A biopsy was taken from the right ovary but not from the left. Exploration of the ileocecal region and the first 20 cm. of the ileum disclosed no Meckel's diverticulum, ileocolitis or ileitis. No nodes were palpable. The appendix was kinked on itself in its middle third. Other than this the entire abdomen was negative."

TABLE 1. *Results of Endocrine Analyses.*

| SUBJECT OF TEST | URINARY 17-KETOSTEROIDS | URINARY ESTROGENS | PITUITARY GONADOTROPHINS |
|---|---|---|---|
| | *mg./24 hr.* | *mouse units/24 hr.* | *mouse units/24 hr.* |
| A.R. | 10.6 | 44- 67 | 48- 96 |
| O.R. | 11.5 | 27- 44 | 48-96 |
| Normal control | 2.0-22.0 | 13-133 | 4- 96 |

FIGURE 2. *Microscopical Section from the Biopsy of the Right Gonad of A.R.*

*The section shows a fetal type of testicular pattern, with early retrogressive changes (postpubertal). Spermatogenesis is entirely absent; the tubules are limited with sertolilike cells having indistinct cytoplasmic margins and ovoid reticular nuclei. The stromal tissue shows a slightly increased fibroblastic reaction, with some hyaline change; interstitial leydig cells are sparse. No ovarian tissue is present.*

The pathological diagnosis was "fetal testicular tissue" (Fig. 2).

A skin biopsy* was reported as showing epidermal nuclei with typical male morphology. This finding was explained as follows:

Few of the epidermal cells have a chromosomal sex mass in addition to the nucleoli, in contrast to the female pattern, in which this mass is common. This mass is usually just beneath the lining membrane of the cell. The female is thought to have this mass because of the XX chromosomal pattern in contrast to the male with the XY pattern (Fig. 3).

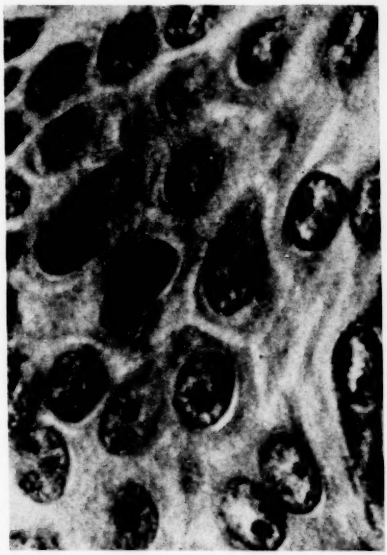

FIGURE 3. *Microscopical Section of the Skin Biopsy (A.R.), Stained with Hematoxylin and Eosin.*

*The epidermal nuclei have a typical male morphology.*

It was now believed that the patient exhibited the complete syndrome of testicular feminization—she was a normal-appearing female with normal urinary gonadotrophins and other hormonal studies, but with male gonads and male morphology in the skin biopsy.

The following abstract was obtained on the patient's 2 sisters†:

O.R., a single, 19-year-old girl, was apparently healthy in all respects except that she had never menstruated. Physical examination showed female contour, with female distribution of pubic and axillary hair, which was scant in growth. The breasts were normal in size; the chest and abdomen were normal. Pelvic examination disclosed a normal vulva and clitoris; the vagina was a blind pouch 3 cm. in depth. No cervix or uterus and no adnexal structures were palpable. Rectal examination was negative. A

*Interpreted by Dr. M. L. Barr.

†Kindly provided by Dr. D. J. Preston.

24-hour study for urinary endocrine levels showed pituitary gonadotrophins, 17-ketosteroids and estrogens of normal levels (Table 1). The patient refused to have any other studies made.

Another sister, M.R., 21 years of age, had been married for 2 years and apparently enjoyed a normal sex life. She desired children, but had never menstruated. Like her sisters, she was apparently a normally developed female. Again, there was normal female hair distribution, the amount of growth again being scanty. Pelvic examination disclosed a normal vulva and clitoris; in addition, however, there was a urethral caruncle, which bled on occasion. The patient spoke of this bleeding as being her menses. Pelvic examination further showed no uterus or adnexa, although the vagina was normal in size. This patient also refused to have any further procedures or studies done.

The literature demonstrates that in 20 per cent of cases of this syndrome reported, cancer of the gonads eventually occurs. This fact was carefully explained to the 3 sisters. In spite of this we were unable to obtain studies on either O.R. or M.R., nor would A.R. give permission for castration.

## Discussion

The cases summarized above are typical of the syndrome described by Morris,[2] Goldberg and Maxwell,[4] Wachstein and Scorza[5] and others. In this syndrome the patients exhibited completely feminine form, without any signs of masculinity. There was no hirsutism, and the hair distribution was typically female, even though it was usually scanty in the axillary and pubic areas. These observations support those of Kaufman, who in 1929 stated "the external habitus follows the external sex parts and not the true sex (testes)."[6]

The breasts are usually normal in size, and on occasion may be even larger than normal; however, the nipples, areolae and ductal tissue may be underdeveloped. The external genitalia are usually normal in appearance, and the vagina can vary from normal size, as in M.R., to a shortened pouch such as that seen in O.R.

As a rule no uterus, cervix, or adnexa are palpable. On occasion the gonads have been reported in the inguinal canal or scrotum. Exploration discloses complete absence or hypoplasia of the uterus, cervix and tubes. The gonadal findings are similar to those in cryptorchid testes, except that there is an increased number of interstitial cells.[4] The seminiferous tubules are immature and sometimes hyalinized. Usually, incomplete spermatogenesis or complete absence of spermatogenesis is demonstrated. Varying amounts of fibrous stroma resembling ovarian tissues are sometimes found.[2] In these cases the gonads may be confused with ovotestes or ovarian neoplasms.

Psychologically, these patients are in all respects definitely female. The libido is normal; there is a desire to be a female psychologically — to menstruate, to marry and to bear children. This desire to menstruate was so prominent in M.R. that she refused, on the advice of her surgeon, to have the urethral caruncle removed because on occasion a few drops of blood came from the caruncle. When this occurred she wore a pad and marked her calendar as though she had a menstrual cycle.

These male pseudohermaphrodites present an interesting problem—namely, the origin of the estrogen. The estrogen is thought to arise either from the adrenal glands or from the testes, and the estrogenic levels are usually normal. Furthermore, it is known that in cases in which castration was performed, there was an increase in urinary gonadotrophin titer, with a decrease in urinary estrogen; clinically, flushes and sweats appeared, and the size of the breasts diminished. The vaginal cytology showed atrophic cells.[3,7] A reversal or disappearance of these manifestations could be brought about by the administration of estrogenic substances.

Experimentally, there is considerable evidence that animal testes are able to produce estrogen. This substance has been extracted from the testes of various species — namely, oxen, stallions and deer.[8] Sertoli-cell tumors of the testes in dogs produce feminization, and from these tumors in dogs estrogen has been extracted. Paschkis, Rakoff and Cantarow[9] state that "it is possible, although not yet definitely proven, that a second testicular hormone may be an estrogen produced by the Sertoli cells."

Increased temperature is considered by some to play a major part in the formation of estrogen by the testes in the intra-abdominal position. Mouse ovaries can be caused to produce androgen if environmental temperature states are altered.[8] This suggests that the abdominal position of the testes in male pseudohermaphrodites might cause an alteration in the physiology of the testes and thus increase their estrogen production. Witschi and Mengart[10] advanced morphologic evidence to substantiate this postulate; against it, however, are the cases of this syndrome in which the testes are in the scrotum.[10]

There are so many conflicting data that many investigators do not believe that there is sufficient histologic evidence to decide just what is the source of estrogen in the testes. Even though we cannot tell exactly the histologic cellular element involved, the testes do produce estrogen.

Further light on the source of estrogen in male pseudohermaphrodites has been thrown on this subject by Green with his experiments on rats.[11] He showed that if estrogen is given to pregnant rats the males in the litter become feminized. It seems probable that excessive amounts of estrogen at a critical period of development will cause stimulation of the fetal structure. Unfortunately, the exact source of excessive estrogen in the human being is not known. One may postulate that it comes from the mother's ovaries, the fetal gonads or the placenta.

This now leads to what happens to these cryptorchid testes, since the occurrence of tumors in this condition is well known. Rea, in 1931, stated that the incidence of tumors is increased fifty times over that of testes that descended.[12] Morris[2] believes that cas-

tration after puberty should be done on these patients; of the 29 cases of pseudohermaphroditism reported by him, malignant change in the gonads developed in 6, or 20.6 per cent. After castration it is recommended that these patients be given estrogen therapy. We do not believe that they should be made into males, because they are feminine by all criteria except the histologic.

A technic to determine the true sex of pseudohermaphrodites has been used recently by Barr[13] — namely, skin biopsy. With this method he has been able to determine the chromosomal type by examining the epidermal nuclei under the microscope.[12-15] In addition, he considers the skin biopsy a useful aid in the differential diagnosis of congenital adrenogenital syndrome and male pseudohermaphroditism in cases in which the clinical findings are equivocal. It is vitally important to recognize the adrenogenital patients early, for they may be benefited by the use of cortisone.

## Summary

The syndrome of testicular feminization in the male pseudohermaphrodite is discussed, and a case of this syndrome is presented. Two other cases occurring in the same family that may be of the same type are described.

A discussion of the possible mechanism of testicular feminization is presented.

The skin biopsy for determination of the chromosomal sex of the individual is discussed, and its importance in these cases emphasized.

We are indebted to Dr. Murray L. Barr, professor of microscopical anatomy, University of Western Ontario, London, Canada, and to Dr. John McLean Morris, associate professor of gynecology, Yale University School of Medicine, for their interest and aid, as well as to Dr. Daniel J. Preston, attending chief, Surgical Department, Delaware Hospital, for supplying the information on the 2 sisters, who were his patients.

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# CARDIORESPIRATORY PROBLEMS IN SEVERE POLIOMYELITIS OBSERVED DURING THE RECENT EPIDEMIC*

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BOSTON

During the 1955 epidemic in Massachusetts more than 400 patients with poliomyelitis were hospitalized at the Massachusetts General Hospital. There were 74 adults requiring respirator management, with 17 fatal cases. Death in acute poliomyelitis that is not the result of obvious airway obstruction, ventilatory insufficiency or some other specific complication has been attributed to "circulatory collapse" secondary to involvement of the medullary vasomotor center[1,2] and, less frequently, to "circulatory collapse" from myocarditis.[2] The observations reported below appear to amend these concepts and suggest other possibilities and empirical methods of management.

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## Presentation of the Clinical Material

An analysis of these 17 fatal cases reveals that 6 patients died from identified causes other than acute poliomyelitis: 2 from massive pulmonary emboli; 1 from a coagulation defect with uncontrolled bleeding; 1 from aspiration of vomitus; 1 from acute airway obstruction; and 1 from cardiac arrest during anesthesia. The remaining 11 patients presented a clinical picture of "circulatory collapse," which in previous years would have been attributed to involvement of the medullary vasomotor center.

The therapy in these 11 patients who died of "circulatory failure" differs, and, accordingly, they can be divided into two groups. In the first group, consisting of 7 patients, all but 1 died within thirty-six hours of entering the respirator, whereas in the second group, consisting of 4 patients, the duration of life was nine to twenty-eight days.

In the first group, who succumbed early, the onset of "circulatory collapse" was characterized by anxiety, apprehension, a dusky, florid appearance, tachycardia and normotension or hypertension. These patients became confused, cold and clammy, with mottled cyanosis, and the majority died with hypotension not responding to nor-epinephrine or plasma-volume expanders.

TABLE 1. *Effect of Various Oxygenation Technics on Blood Gas Analyses in a Patient Demonstrating Hypoxia in Spite of Adequate Ventilation.*

| Ventilation Mechanism | Arterial Oxygen | Carbon Dioxide | pH | Ventilation | Blood Pressure |
|---|---|---|---|---|---|
| | % | *milliequiv./liter* | | | |
| Respirator | 63 | 23.5 | 7.42 | Adequate | Normal |
| Respirator with oxygen | 98 | 23.0 | 7.44 | Adequate | Normal |
| Jefferson ventilator | 97 | 26.0 | 7.35 | Adequate | Normal |
| Jefferson ventilator | 68 | 33.0 | 7.43 | Inadequate | Normal |
| Jefferson ventilator | 98 | 34.0 | 7.55 | Inadequate | Normal |

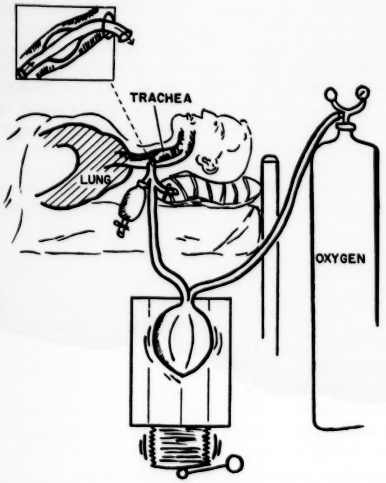


FIGURE 1. *Diagram, Showing Respiration by Intermittent Positive and Negative Endotracheal Pressure Delivered by the Jefferson Ventilator.*
*A tracheostomy and a cuffed endotracheal tube are required, and the percentage of oxygen in the insufflated air can be varied according to the needs of the patient.*

Ventilation studies in these patients indicated that each was obtaining a tidal volume equal to, or greater than, that suggested as optimal by the nomogram of Radford et al.[4] Serum electrolytes were either normal or compatible with a respiratory alkalosis, indicating that in each case ventilation was adequate for the removal of carbon dioxide. Electrocardiograms taken in 3 patients revealed nonspecific ST-segment and T-wave changes compatible with myocardial hypoxia.

In the second group, who succumbed after one to four weeks, studies of arterial oxygen saturation were performed. It was found that arterial oxygen unsaturation was present to a marked degree in the normotensive or hypertensive phase, and that with the onset of hypotension the saturation was considerably further diminished. Furthermore, arterial oxygen unsaturation persisted, despite restoration of blood pressure with nor-epinephrine and optimal tidal exchange. An illustrative case is represented in Table 1.

While this patient was in the tank respirator marked cyanosis developed, with an arterial oxygen saturation of 63 per cent, and he subsequently became hypotensive. Though nor-epinephrine restored the blood pressure to normal, the cyanosis persisted. On the other hand, with the administration of 100 per cent oxygen into the tracheostomy the saturation was increased to 98 per cent, and normotension was restored without nor-epinephrine. At this point, the patient was transferred to the Jefferson ventilator, which is described below. Though the patient subsequently became hypoxic even on the Jefferson ventilator with 100 per cent oxygen, this was gradually reversed by an increase in the magnitude of positive pressure, and normotension was maintained despite the presence of hypercapnia due to ventilatory insufficiency.

TABLE 2. *Effect of Various Oxygenation Technics on Blood Gas Analyses in a Second Patient Demonstrating Hypoxia in Spite of Adequate Ventilation.*

| Ventilation Mechanism | Arterial Oxygen | Carbon Dioxide | pH | Ventilation | Blood Pressure |
|---|---|---|---|---|---|
| | % | *milliequiv./liter* | | | |
| Bag breathing | 94.5 | 26.0 | 7.38 | Adequate | Normal |
| Respirator | 59 | 29.0 | 7.40 | Adequate | Hypotensive |
| Respirator with oxygen | 93 | 27.0 | 7.48 | Adequate | Normal |
| Respirator | 56 | 30.0 | 7.43 | Adequate | Normal |

The Jefferson ventilator (Fig. 1) is an automatic ventilating machine that aerates the patient by intermittent positive and negative intratracheal pressure. Because the patient can be placed in a bed, nursing care is much simpler, and frequent changes in position are possible. Thus, hypostasis is more readily controlled, bacterial infection is more easily combated because postural drainage can be initiated, and decubitus ulcers can be prevented or more effectively managed. The psychologic gain from such a change is also worth while.

On the basis of arterial oxygen determinations done on 20 of the 53 surviving patients, it appears that the

maintenance of adequate oxygenation by supplementary technic contributed materially to the survival of at least 7 of these patients. A case illustrative of this group is represented in Table 2.

In this patient marked cyanosis with hypotension developed on the fourth respirator day, and he required nor-epinephrine for maintenance of blood pressure. At that time, bag breathing of 100 per cent oxygen with an anesthesia machine maintained 95 per cent saturation whereas return to the tank respirator resulted in a fall in saturation to 59 per cent. With the administration of 100 per cent oxygen into the tracheostomy and with the patient still in the respirator, 93 per cent saturation was obtained, and the need for nor-epinephrine eliminated. A brief trial in the respirator without supplementary oxygen again resulted in 56 per cent saturation. On this occasion oxygen was given before hypotension reappeared. The patient was then transferred to the Jefferson ventilator, and adequate saturation was effectively maintained with 60 per cent oxygen and later with room air.

### Presentation of Pathological Material

Tables 3-5 present the gross and microscopical findings in each of the three groups of patients: those dying of complications of their disease other than "circulatory collapse"*; those dying of "circulatory collapse" without oxygen therapy; and those dying of "circulatory collapse" despite oxygen therapy.

The lung weights in the 5 patients dying of complications other than "circulatory collapse" (Table 3) varied, depending on the complication, but in no case was pulmonary edema or congestion a prominent pathological finding. The lung weights in the 7 patients dying with "circulatory collapse" without oxygen therapy (Table 4) were uniformly increased, ranging from two to four times the normal weight. The principal pathological finding (Fig. 2) was pulmonary edema and congestion. The lung weights in the 4 patients who died in spite of oxygen therapy (Table 5), again, were elevated, primarily because of the presence of bronchopneumonia and not pulmonary edema and congestion. Early in their illness, 3 of these 4 patients had been carried through a period of arterial oxygen unsaturation, presumably owing to pulmonary edema, with supplementary intratracheal oxygen. There is a striking absence of pulmonary edema in this group in contrast to the predominance of pulmonary edema in the group dying of "circulatory collapse" without benefit of adequate oxygen-

Table 3. *Deaths Due to Complications Other than "Circulatory Failure."*

| Patient | Days in Respirator | Lung Weight | Microscopical Findings in Lung | Heart | | Microscopical Findings in Heart |
|---|---|---|---|---|---|---|
| | | | | Weight | Ventricular Thickness | |
| | | *gm.* | | *gm.* | *mm.* | |
| A.G. | 2 | 1400 | Pneumonia | 320 | 4/17 | Slight myocarditis |
| D.B. | 20 | 650 | Focal hemorrhage | 360 | 3/13 | Negative |
| G.D. | 24 | 2200 | Hemorrhage & congestion | 300 | 3/12 | Negative |
| R.S. | 24 | 950 | Emboli & congestion | 400 | 3/13 | Negative |
| F.R. | 37 | 590 | Emboli | 260 | 4/15 | Negative |

Table 4. *Deaths Due to "Circulatory Failure" without Oxygen Therapy.*

| Patient | Days in Respirator | Lung Weight | Microscopical Findings in Lung | Heart | | Microscopical Findings in Heart |
|---|---|---|---|---|---|---|
| | | | | Weight | Ventricular Thickness | |
| | | *gm.* | | *gm.* | *mm.* | |
| E.N. | 2 | 930 | Edema & congestion; early pneumonia. | 220 | 2½/11 | Negative |
| E.K. | 2 | 1100 | Edema & congestion | 330 | 4/14 | Negative |
| L.G. | 7 | 1000 | Edema & congestion; slight pneumonia. | 350 | 4/12 | Negative |
| C.H. | 2 | 1600 | Edema & congestion | 420 | 2/15 | Negative |
| H.R. | 1 | 2230 | Edema & congestion | 360 | 3/15 | Negative |
| M.R. | 2 | 1840 | Edema & congestion; early pneumonia. | 400 | 2½/15 | Myocarditis |
| R.H. | 2 | 1890 | Edema & congestion; early pneumonia. | 330 | 2½/12½ | Negative |

*Six patients died of complications other than "circulatory collapse"; no post-mortem examination was performed in the patient who died from aspiration of vomitus.

ation. This suggests that the pulmonary edema and congestion in those patients dying of "circulatory collapse" without oxygen therapy is a reversible phenomenon if arterial oxygen saturation is restored.

There were no apparent cardiac abnormalities except that myocarditis was present microscopically in 2 cases. In 1 of these, the findings were probably due to cardiac massage after arrest twenty-four hours before death.

## Discussion

In the cases presented it was impossible to obtain adequate arterial oxygen saturation despite optimal ventilation. Increasing the concentration of oxygen in the inspired or insufflated air restored arterial oxygen to normal levels. Since the pulmonary edema was the major pulmonary finding on post-mortem examination, an alveolar-arteriolar diffusion defect seems the most likely explanation for the occurrence of the original arterial oxygen unsaturation.

The etiology of the diffuse pulmonary edema, which was frequently hemorrhagic, remains obscure. Regardless of its origin, the pulmonary edema and progressive arterial oxygen unsaturation leads to "circulatory collapse." The concept of peripheral vasomotor collapse as a direct consequence of involvement of the medullary vasomotor center does not account for the presence of arterial oxygen unsaturation during the normotensive or hypertensive phase. The failure of nor-epinephrine to restore saturation even when it effectively reverses hypotension is also against a primary peripheral vascular collapse. The observations presented suggest that the pulmonary edema is a major factor in the production of the "circulatory collapse." The effectiveness of increased concentrations of oxygen in reversing the arterial oxygen unsaturation and hypotension is in accordance with this concept.

Further and more fundamental investigations are required to ascertain the etiologic factors in the production of pulmonary edema in acute poliomyelitis. Alterations in circulatory dynamics induced by the action of the tank respirator, the effect of hypoxia on myocardial proficiency, the production of pulmonary edema by specific neurologic lesions and changes in pulmonary capillary permeability are possible mechanisms that might be studied profitably. The tank respirator and positive-pressure ventilator need further comparative evaluation.

## Summary

Correlative clinical observations, post-mortem findings and blood gas analyses were performed in 16 fatal cases of acute poliomyelitis.

Eleven of these cases presented a syndrome of pulmonary edema, hypoxia and hypotension indistinguishable from the classic description of "circulatory collapse" in acute poliomyelitis.

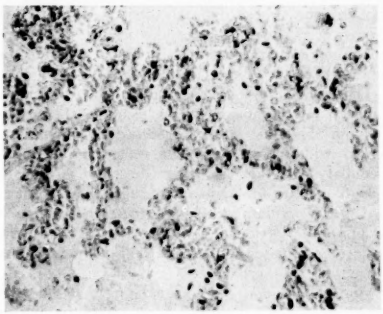

Figure 2. *Microscopical Section of the Pulmonary Parenchyma, Showing Marked Congestion of the Septal Capillaries, with Edema of the Alveolar Spaces.*

In 4 of these patients and 7 of those still surviving, the syndrome was reversed by an increase in the concentration of oxygen in the inspired or insufflated air.

The implication of these observations in relation to the concept of medullary vasomotor collapse is discussed, and the need for further fundamental investigation emphasized.

Table 5. *Deaths Due to "Circulatory Failure" in Spite of Oxygen Therapy.*

| Patient | Days in Respirator | Lung Weight | Microscopical Findings in Lung | Heart | | Microscopical Findings in Heart |
|---|---|---|---|---|---|---|
| | | | | Weight | Ventricular Thickness | |
| | | *gm.* | | *gm.* | *mm.* | |
| L.M. | 9 | 1290 | Edema & congestion; pneumonia. | 400 | 5/15 | Negative |
| D.M. | 30 | 1090 | Pneumonia | 360 | 4/15 | Negative |
| H.T. | 22 | 1431 | Pneumonia | 300 | 3/14 | Negative |
| I.L. | 10 | 890 | Early pneumonia; atelectasis. | 290 | 4/14 | Negative |

We are indebted to Dr. Walter Bauer for his valuable suggestions and encouragement and to the house staff, visiting physicians and consultants for assistance.

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## MEDICAL PROGRESS

# GLUCAGON: PHYSIOLOGIC AND CLINICAL CONSIDERATIONS*

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ALTHOUGH glucagon (hyperglycemic glycogenolytic factor) was discovered and named thirty-four years ago, it has yet to achieve unqualified acceptance as a hormone.[1,2] With one possible exception, no clinical disorder attributable to a deficiency of glucagon has been identified.[3] Nor is there general agreement concerning the site of origin of this substance.[4,5]

These objections, however, are not as decisive as might at first be imagined. For example, there is no question about the hormonal nature of epinephrine; yet no syndrome referable to a deficiency of adrenal medullary secretion has been described. And, although the site of origin of glucagon has not been settled to everyone's satisfaction, there is considerable circumstantial evidence to support the view that glucagon originates in the alpha cells of the islands of Langerhans of the pancreas.

Moreover, evidence is accumulating that glucagon production in the pancreas is increased by insulin treatment,[6] and in the obesity-hyperglycemia syndrome of mice.[7] Physiologic studies have shown that the pancreas releases increasing amounts of a hyperglycemic factor (to date, indistinguishable from glucagon) in response to hypoglycemia[8] and treatment with growth hormone and ACTH.[9,10] At the same time, a number of recent clinical and experimental studies have given rise to "second thoughts" about glucagon, particularly concerning its alleged role as an "insulin antagonist."[11]

The history of glucagon from its discovery by Kimball and Murlin[12] in 1923 to its purification and crystallization by Staub, Sinn and Behrens[13] in 1953 has been well reviewed by Foà,[14] Pincus,[15] de Duve[16] and others.[17-19] Nevertheless, a brief outline seems worth reiterating, if only as further vexatious proof that hindsight is better than foresight.

### HISTORY

Soon after the discovery of insulin by Banting and Best in 1921, Collip showed that a transient hyperglycemia preceded the hypoglycemia induced by pancreatic extracts prepared by the Banting–Best technic.[20] Approximately a year later Murlin et al.[21] announced that from pancreatic extracts they had obtained a fraction ". . . with the power to act in just the opposite way to insulin; namely to raise the blood sugar both of normal and diabetic animals enormously." No details were given in the first paper, but in a subsequent communication Kimball and Murlin[12] reported that by acetone precipitation of pancreatic extracts they had obtained a preparation that when given subcutaneously to 2 depancreatized dogs had raised the blood sugar markedly. This agent they named "glucagon." In retrospect, this finding seems somewhat vitiated by their statement that by means of the same procedure they had separated a similar hyperglycemic substance from cat's muscle and from yeast.

In 1929, Collens and Murlin,[22] in a series of well constructed experiments, showed conclusively that when "insulin" was injected into the portal vein a marked early hyperglycemia ensued. A comparable hyperglycemia did not occur when the same amount of insulin was injected into a peripheral vein. In the discussion of their findings Collens and Murlin postulated that the sudden introduction of insulin into liver caused a rapid glycogenolysis. Their tentative conclusion was that insulin was a glycogenolytic agent.

Curiously, in the light of Murlin's earlier work with glucagon, no mention was made of the possibility that glucagon was present in the insulin preparation as a contaminant. During the same year, Bürger and Kramer,[23] in Germany, also performed studies showing that the transient hyperglycemia that followed injection of certain insulin preparations was due to a glycogenolytic action on the liver. A number of subsequent studies proved that insulin treatment could lower liver glycogen.[24-27] This occurred even if glucose was administered simultaneously to prevent hypoglycemia.[27]

The repeated finding that insulin treatment can lower liver glycogen even in the absence of hypoglycemia was, for a time, a source of considerable confusion in the literature on carbohydrate physiology. Many workers understandably found it difficult to reconcile a glycogenolytic effect of insulin on liver with its known capacity to restore liver glycogen in depancreatized animals. Moreover, Taubenhaus, Levine and Soskin[28] had shown by in vitro studies that insulin inhibits glycolysis in the dog's liver. By hepatic-vein catheterization, Sherlock and her associates demonstrated that insulin administration diminishes the output of glucose by the liver.[29]

Probably many of the contradictory findings concerning the effect of insulin on liver glycogen resulted from the presence of glucagon as a contaminant in insulin preparations.

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In 1926 Abel[30] crystallized insulin, and when Geiling,[31] in 1930, injected Abel's preparation he was unable to demonstrate any hyperglycemic-glycogenolytic effects. In 1934 Scott[32] described another method of preparing insulin that was quite adaptable for commercial use and was subsequently taken up by manufacturers in the United States. Dotti, using Scott's preparation in 1936, found that certain rabbits given insulin subcutaneously displayed an early transient hyperglycemia of approximately 15 mg. per 100 ml. above fasting levels.[33] At the time these effects were believed to be insulin induced.

In 1939 Lundsgaard and his associates[34] compared the Scott preparation with insulin crystallized by Abel's method in terms of their respective effects on the glucose output of the isolated perfused liver. The Scott insulin caused a sudden increase in the glucose concentration of the perfusing blood; the Abel preparation added to the perfusate did not interrupt the rate of fall of the glucose concentration of the perfusing blood.

Although these findings were suggestive, to say the least, the possibility that a glycogenolytic contaminant was present in insulin, as suggested by Bürger and his associates[35] in Germany, apparently did not arouse widespread interest. It was not until de Duve and his associates at Louvain reopened studies on glucagon in 1945 that the subject revived.[36] They demonstrated the presence of "glucagon" in American commercial insulin, prepared by the Scott method, and its absence in the Danish "Novo" insulin. First estimates of the glucagon contamination of insulin preparations placed its concentration at 1 to 10 per cent.[37,38] However, later and more accurate studies have shown that it is present in various American crystalline preparations in amounts ranging from 0.3 to 0.5 per cent.[39]

In 1948 Sutherland and Cori[40] showed that glucagon increases the concentration of active phosphorylase in liver slices. When glucagon is added to liver slices more rapid liberation of glucose occurs than in a control preparation. In 1953, Staub and his associates[13] at the Lilly research laboratories separated glucagon from insulin by selective precipitation and isolated it in crystalline form.

## Chemical Properties and Site of Origin

When Kimball and Murlin described their discovery of a hyperglycemic factor in aqueous extracts of pancreas, virtually nothing was known of its chemical nature. It was not until 1935 that chemical studies on glucagon were reported as indicating that it was a protein very closely related to insulin.[41] Although physiologic and biochemical studies on glucagon continued in increasing number during subsequent years, this material was never available in sufficiently purified form to permit extensive characterization of the molecule until 1953, when Staub, Sinn and Behrens announced that they had purified and crystallized glucagon.

In a later report, Staub and his associates described the properties of purified glucagon in more detail.[42] They found that glucagon is a protein of fairly typical amino acid composition. Its molecular weight was calculated to be 4200. Glucagon differs from insulin in several important respects. Cystine, proline and isoleucine cannot be detected in glucagon although they are present in insulin. Glucagon, however, contains considerable amounts of methionine and tryptophane, both of which are absent in insulin. Like insulin, glucagon is more stable at acid pH values; if kept in the cold in insulin-diluting fluid at pH 3 it retains its hyperglycemic activity for many months. In contrast to insulin, glucagon can crystallize in the absence of zinc or other metals. Glucagon crystallized by the Staub method contains less than 0.01 per cent of zinc. As Staub et al. point out, the chemical and physicochemical properties of the crystalline protein prove that glucagon is an entity distinctly different from insulin. The possibility of its being a degradation product of insulin is ruled out by the amino acid composition of glucagon.

Proof of the site of origin of glucagon is still lacking. It appears that glucagon cannot arise in the beta cells since this substance is extractable from pancreases in which the beta cells have been destroyed by alloxan. Many workers believe the site of origin of glucagon to be in the alpha cells, and possibly in cells resembling alpha cells in the gastric and duodenal mucosa.

Two recent reviews[43,44] have dealt extensively with the role of the pancreatic alpha cells in the production of glucagon. Volk, Lazarus and Goldner,[43] in their review, concede that the alpha cells are a morphologic entity with a secretory function. However, they describe experiments of their own that show that extracts from the pancreas of either normal or alloxanized dogs, in which the alpha cells almost entirely disappeared after cobalt administration, still contain apparently normal quantities of a hyperglycemic principle. Fodden and Read[45] also found that pancreas from rabbits treated with cobaltous chloride (which produces a short-lasting destruction of pancreatic alpha cells) contained an appreciable quantity of material with hyperglycemic activity. However, rabbits treated with synthalin A (another substance toxic for alpha cells) had very little hyperglycemic activity in the pancreas. Fodden and Read concluded that in cobalt poisoning the hyperglycemic material is retained in the pancreas whereas after synthalin A treatment it is not.

In a recent study, Bencosme, Liepa and Lazarus[46] made use of the fact that most of the uncinate process of the dog pancreas is devoid of alpha cells, whereas such cells are found in the remainder of the organ. Extracts of the portion of the pancreas devoid of alpha cells showed virtually no hyperglycemic activity, even when large aliquots of pancreatic material were used. This finding lends strong support to earlier

studies suggesting that the origin of glucagon is in the alpha cells.

The evidence that certain extrapancreatic cells of the enterochromaffin system are a source of glucagon is less convincing.[44] The similarities between these cells and the pancreatic alpha cells have been shown to be superficial. The two cell types differ histochemically and in their response to "alphacytotoxic" substances such as cobaltous chloride and synthalin A. Moreover, it is possible that the hyperglycemic-glycogenolytic material extracted from extrapancreatic cells resembling alpha cells is an epinephrinelike substance with an action similar to that of glucagon on liver slices.

## Physiology

The status of glucagon as a true hormone has been questioned on several occasions.[1,2] Indeed, it has been difficult to find for glucagon a definitive role in carbohydrate homeostasis. Depancreatized animals and human subjects who presumably suffer from a glucagon deficiency have not displayed gross metabolic abnormalities that could not be corrected by use of insulin. On the other hand, after surgical extirpation of the pancreas, patients require less insulin for regulation and are less resistant to ketosis than many persons in whom diabetes develops spontaneously.[47]

Foà and his co-workers[8] have performed crosscirculation experiments in dogs that suggest that the pancreas secretes a hyperglycemic substance in response to insulin-induced hypoglycemia. Sherlock et al.,[48] by means of hepatic-vein catheterization in man, have shown that when insulin is administered hepatic glucose output is immediately decreased. Later, apparently in response to the hypoglycemia, the liver releases extra glucose, and the blood sugar level is restored to normal. This increased glucose output precedes in time the increased hepatic blood flow and lactic acid output that occur when epinephrine is secreted. Hence, these changes apparently are not due to epinephrine action. They may be in part an effect of glucagon, as postulated by Foà, or, alternately, the liver may release glucose in direct response to hypoglycemia without any need for glucagon intervention. Administration of hexamethonium bromide, which is supposed to block sympathetic impulses to the adrenal medulla, does not delay the return of blood glucose levels to normal after insulin-induced hypoglycemia.[49] Accordingly, as Bearn, Billing and Sherlock point out, other factors capable of increasing hepatic glucose output must be considered — among them, glucagon.

It is interesting, in view of the findings of Foà and of Sherlock, that in animals chronically treated with insulin the glucagon content of the pancreas is increased.[6]

Apparently, growth-hormone administration may elicit secretion of a hyperglycemic factor from the pancreas. Bornstein, Reid and Young[50] have shown that the blood from the pancreaticoduodenal vein of growth-hormone-treated cats contains a blood-sugar-raising substance that is not demonstrable in the femoral-vein blood from the same animals. With his crosscirculation technic Foà[9] has obtained similar findings. Fodden and Read[10] were able to extract from the pancreatic venous blood of the dog a protein substance with a biologic activity similar to that of glucagon. Its total yield was uniform and was increased only slightly by the presence of alloxan diabetes. However, almost a threefold increase resulted from preparatory treatment with pituitary growth hormone, or ACTH. Genetically obese mice, which are said to contain significantly more glucagon in their pancreases than normal mice, respond with marked hyperglycemia to growth-hormone administration whereas their nonobese litter mates show no significant hyperglycemic response to growth hormone.[51]

It was inevitable that the hyperglycemic properties of glucagon would make it suspect as a substance with some sort of "antagonism" to insulin.[16,52] This suspicion was reinforced when certain experiments suggested the possibility of a tropic effect of growth hormone upon glucagon secretion. However, when an attempt is made to understand what is meant by "antagonism" applied to the physiologic action of glucagon, serious difficulties arise. The term "antagonism" is often used rather loosely in discussions of biologic phenomena. For example, because the sympathetic and parasympathetic nerves may have "opposing" effects on smooth muscle, these systems are frequently referred to as "mutually antagonistic." Actually, the parasympathetic and sympathetic nerves act synergistically, and to think of them as being antagonistic creates a barrier to the understanding of the autonomic nervous system. Similarly, the concept of "antagonism" has been applied indiscriminately to metabolic phenomena and also with frequent obscuration of the facts.

The action of insulin about which there is most general agreement is that it somehow facilitates entry of glucose into cells.[53] This may be its only action. If glucagon is to be considered in any sense an antagonist to insulin, or "diabetogenic," it must interfere in some way with the effect of insulin on the rate of transfer of glucose into cells. There is evidence that growth hormone is antagonistic to insulin in this sense.[54] The evidence with glucagon has been contradictory.

J. L. Rodriguez-Candela[55] has reported that the "hyperglycemic factor" interferes with the glucose uptake of the isolated rat diaphragm. However, subsequent studies by Smith and Young[56] did not confirm Rodriguez-Candela's findings. These investigators were unable to demonstrate any clear-cut effect of glucagon on rat diaphragm.

Tyberghein[57] gave hyperglycemic factor by intravenous infusion to rabbits for six hours and at the same time administered 30 units of insulin every

ninety minutes during this period, 4 injections in all. At the end of the six hours the liver glycogen level was the same as that in control animals that had been treated for six hours with an intravenous infusion of saline solution and no insulin. Muscle glycogen content remained unchanged. Nor was there an increase in nitrogen excretion, which would have occurred if gluconeogenesis had been active. These experiments suggested that glucagon might antagonize the effect of insulin both in the liver and in the peripheral tissues. Respiratory-quotient studies were not reported by Tyberghein, but these might have helped support his thesis of an anti-insulin action of glucagon.

Drury, Wick and Sherrill[58] studied the effect of glucagon injection on the oxidation and rate of transfer into cells of radioactive glucose in rabbits that had been both eviscerated and nephrectomized. They reported some degree of inhibition of glucose uptake by the extrahepatic tissues after glucagon administration. Apparently, there was no decrease in rate of glucose oxidation. They concluded that glucagon acts as an insulin antagonist. There is some question, however, whether studies on extrahepatic glucose utilization by hepatectomized animals are necessarily pertinent to utilization of glucose by the peripheral tissues of intact animals. Apparently, the presence of the liver is needed for efficient glucose assimilation by tissues; moreover, when the liver is absent, other substrates tend to displace glucose as a source of fuel for the extrahepatic tissues.[59,60]

de Duve,[16] in his comprehensive review of glucagon, described glucagon as an insulin antagonist "at least as potent as epinephrine," and the suggestion has been made that the glucagon in many commercial preparations of insulin decreases its clinical effectiveness and alters the assay results for insulin potency.

To explore this possibility, Root et al.[61] added as much as 100 per cent by weight of glucagon to a glucagon-free insulin preparation and tested the mixture for potency. They found that the glucagon had no effect on the mouse convulsion assay for insulin. Experiments with a similar mixture on rabbits and mice showed that added glucagon did not affect the maximal insulin hypoglycemia, which normally reaches its peak sixty to ninety minutes after injection.

Ingle[62] was unable to demonstrate any effect of glucagon on glucose disposal in eviscerated rats. Van Itallie, Morgan and Dotti[63,64] studied the effect of glucagon on peripheral glucose uptake in man, using peripheral capillary-venous glucose differences as an index of glucose assimilation. They compared hyperglycemias induced by intravenous infusions of glucagon with similar hyperglycemias induced respectively by intravenous and oral administration of glucose, the latter in combination with a small amount of subcutaneously injected epinephrine. Although the epinephrine markedly decreased peripheral glucose uptake, glucagon had no such inhibitory effect and, indeed, may have enhanced glucose utilization. It was also shown that blood glucose levels fell toward normal and that peripheral glucose uptake remained active during prolonged glucagon infusion. Similar findings were reported by Elrick[65,66] and Bondy.[67]

Elrick, Hlad and Witten[66] have recently reported studies suggesting that glucagon causes an increase in the peripheral utilization of glucose and that this increased glucose utilization is greater than that observed with the hyperglycemia produced by intravenous administration of glucose alone.

Thus, it appears that glucagon does not, in fact, interfere with the effect of insulin on glucose transfer into extrahepatic cells. In the sense that glucagon raises blood glucose whereas insulin lowers it, glucagon is an "anti-insulin" factor. By the same token, ingested carbohydrate would have to be called an anti-insulin substance, and this would reduce the concept of insulin antagonism to nonsense. If insulin can be considered a stimulant to glycogenesis, glucagon might be called an anti-insulin factor to the extent that it is glycogenolytic. However, even here the point is a labored one since the two substances act on different systems in the liver. For the sake of clarity it seems desirable to reserve terms such as "insulin antagonism" to describe situations in which the effect of insulin on cellular disposal of glucose is interfered with. Substances that raise the blood sugar without impairing glucose assimilation would not then be so classified.

Thus, although the possibility exists that glucagon either directly or indirectly has an enhancing effect on peripheral glucose utilization, no conclusive evidence is at present available that glucagon has any primary physiologic action other than to stimulate hepatic glycogenolysis.[68,69]

## Diabetes Mellitus

It has been noted that patients who survive total pancreatectomy require relatively small amounts of insulin to control their blood sugar. Yet, when insulin is withheld, ketosis tends to develop in such patients.[47] In this respect, pancreatectomized persons resemble young labile diabetic patients. In contrast, certain obese and middle-aged diabetic patients may require appreciable amounts of insulin to control their hyperglycemia and yet ketosis does not develop readily when insulin is withdrawn.[70]

Similarly, insulin sensitivity is greater in depancreatized dogs than in dogs treated with alloxan, and the dog without a pancreas becomes more ketotic than the alloxanized dog when insulin is withheld.[71,72] The effect of pancreatectomy on insulin requirement does not seem to be due to faulty absorption of foodstuffs because of lack of pancreatic enzymes since ligation of the pancreatic ducts does not diminish the high requirement for insulin of the alloxan-diabetic dog.[73]

These findings suggest that the pancreas may pro-

duce a substance that increases the insulin requirement, and protects against ketosis. Thus, it is of interest to consider whether glucagon secretion might account for these two phenomena. Ferner[52] has gone so far as to suggest that a "metabolic equilibrium" exists between alpha and beta cells in man, and that an absence of glucagon results in hypoglycemia while an excess of glucagon results in diabetes. To support his contention, Ferner has performed cell counts on human pancreases. He has reported that in the diabetic patient a preponderance of alpha cells can be demonstrated and believes that this finding has etiologic significance.

In the obese-hyperglycemic mouse (an animal with traits in common with the middle-aged obese diabetic patient), Mayer, Andrus and Silides[74] have found a marked relative increase in the number of alpha and beta cells of the pancreatic islets. When such animals are treated with diethyldithiocarbamate (DEDTC), a substance supposed to injure alpha cells selectively, they promptly lose their hyperglycemia and insulin resistance. Treatment with growth hormone no longer elicits hyperglycemia. Unfortunately, Mayer et al. were unable to demonstrate actual morphologic changes in the alpha cells after DEDTC treatment and the effects of the treatment were lost after two weeks. Other studies on the obese-hyperglycemic mice indicate that they have both an increased liver glycogen content and turnover,[75] and an increased hepatic phosphorylase activity.[76]

Some of these findings might be interpreted as supporting the concept that glucagon secretion is responsible for the metabolic differences between alloxanized and depancreatized animals. It is conceivable that glucagon by its glycogenolytic action on liver increases glycogen turnover and thereby increases the insulin requirement. This would presumably entail more active gluconeogenesis from protein, an activity that should be reflected in the nitrogen balance. Yet studies involving comparison of alloxan-diabetic rats with depancreatized rats excreting comparable amounts of glucose have not shown differences in nitrogen excretion between the two groups even while the depancreatized animals were displaying a more marked ketonuria.[77]

It has not been possible in the relatively short-term experiments reported to date to demonstrate that glucagon has antiketogenic properties. Indeed, glucagon administration has been shown to increase ketonemia in some cases, presumably by depleting liver glycogen.[78,79]

Since a long-acting glucagon preparation is not yet available it cannot be determined whether experiments performed with the short-acting material for relatively brief periods are pertinent to the problem of identifying the cause of the metabolic differences between depancreatized and alloxan-diabetic animals.

At present, knowledge about the metabolic effects of glucagon does not seem to explain satisfactorily the physiologic differences between alloxanized and depancreatized animals.

## Types of Diabetes

For many years, two major types of diabetes have been identified by clinicians. Although agreement about all the criteria to be used has been far from complete, there are several characteristics that most of the classifying systems have in common. For example, there is general concurrence that one type is characterized by a widely fluctuating blood sugar, insulin sensitivity and a tendency for ketosis to develop readily. The other type displays a more stable blood sugar, some degree of resistance to insulin and considerable resistance to ketosis. Although the two groups admittedly overlap, the former group is made up primarily of children and young adults, and the latter principally of middle-aged persons who are usually obese. These two types were named in France *diabète maigre* and *diabète gras*. Himsworth[80] has divided the two groups according to the response of the patient to the insulin-glucose tolerance test. Lawrence[70] has given the name "lipoplethoric diabetes" to the variety observed in middle-aged obese persons, and has used the term "insulin-deficient diabetes" to describe the younger, labile diabetic patient in whom ketosis tends to develop readily. By means of hepatic-vein catheterization, Sherlock[18] has differentiated diabetic patients in accordance with their hepatic response to insulin.

A number of investigators have attempted to determine whether the hyperglycemic responses to glucagon could be correlated with any clinical feature of the disease. Kirtley and his co-workers[81] administered glucagon by intravenous infusion to stable and unstable diabetic patients and followed blood glucose changes. In their series, stable and unstable patients had distinctive responses to glucagon. The so-called stable diabetic patient had a greater and more prolonged rise in blood sugar and a lesser fall in serum inorganic phosphate than the unstable. The authors attributed these dissimilarities to differences in liver glycogen content between the two groups and postulated that some of the characteristics of unstable diabetic patients might derive from a low liver glycogen content.

More recently Alivisatos and McCullagh[82] found that in patients with "brittle" diabetes given glucagon there was a distinctly greater rise in blood sugar than that in normal persons or patients with stable diabetes.

Hubble[83] has reported studies involving comparison of the response to glucagon in unselected diabetic patients with the response to the Himsworth insulin-glucose tolerance test, the insulin tolerance test and the glucose tolerance test. He found that the response to glucagon gave no correlation with age group but that the obese diabetic patient tended to show blood sugar responses in the higher ranges. However, the

response to glucagon correlated poorly with the Himsworth insulin-glucose ratio.

Because of the inconsistent results obtained by various groups concerning the hyperglycemic responses of stable and unstable diabetic patients to glucagon, it is difficult to regard glucagon-induced hyperglycemia as a useful method for distinguishing between the two clinical forms of diabetes or even for throwing light on the underlying physiology of these two diabetic variants. The work of Lawrence and his co-workers suggests that the degree of insulin deficiency per se may distinguish stable from unstable patients whereas the work of Sherlock and her collaborators indicates that the sensitivity of the liver to insulin regarding glucose uptake may be an important consideration. Neither of these factors has been shown to be associated with a deficiency of liver glycogen.

Probably, glucagon-induced hyperglycemias are not particularly reliable indexes of liver glycogen content. Although the hyperglycemic response to glucagon appears to be generally proportional to liver glycogen content, as Root[84] has shown in rabbits, it is not a sensitive enough procedure to be clinically useful. Van Itallie and Bentley[85] compared the hyperglycemic responses to intravenous infusion of glucagon in patients with severe parenchymal liver disease with the responses in normal subjects. Although the normal subjects showed a more pronounced hyperglycemia there was considerable overlap between the two groups, and when the means of the various points of the response curves were compared the differences were statistically significant only during the hypoglycemic phase, which occurred after the end of glucagon infusion. It was pointed out that glucagon-induced hyperglycemia is ordinarily associated with active utilization of the released glucose by the peripheral tissues. Hence, the glycemic level represents a resultant of two variables: rate of hepatic glycogenolysis and rate of peripheral glucose assimilation. Therefore, it is impossible to judge from isolated determinations of glucose concentration in venous blood whether a "response" to glucagon is poor because of intense peripheral utilization of glucose or because of deficient stores of liver glycogen or some combination of the two.

It was shown that when a small amount of epinephrine is administered subcutaneously before glucagon injection the confusing variable of peripheral utilization is minimized and the hyperglycemic response greatly accentuated. Under these circumstances the hyperglycemic response to glucagon appears to provide a more valid basis for estimating liver glycogen content.

## Glucagon Deficiency

McQuarrie and his associates[86] have described 3 cases of spontaneous hypoglycemia in children that may have been due to glucagon deficiency. All occurred in one family, and each of the children began to have symptoms, including convulsions, during the first year of life. When partial pancreatectomy was performed on 2 of the patients to relieve the intractable hypoglycemia, it was found that the pancreatic islets were devoid (or nearly devoid) of alpha cells, as demonstrated by Gomori's special stain for islet cells. Extensive testing failed to yield evidence of adrenal, pituitary or hepatic disease in any of the siblings.

Even after partial pancreatectomy had been performed in 2 of the children the blood glucose tended to fall to low levels, and hypoglycemic symptoms returned. ACTH therapy was then tried and proved to be effective in controlling the hypoglycemia. In 1 child the tendency for severe hypoglycemia to develop disappeared after a year of ACTH treatment and did not recur even after the hormone was stopped.

## Glucagon Excess

Recently, Zollinger and Ellison[87] reported 2 problem cases of benign peptic ulceration of the upper jejunum associated with extremely high gastric acid production, as measured over a twelve-hour period. In both cases, gastric hypersecretion could not be controlled by the usual surgical means, and marginal ulceration recurred until total gastrectomy became mandatory. Of interest was the fact that a pancreatic adenoma containing no beta cells and with neither clinical nor laboratory evidence of insulin production was found at autopsy in 1 patient, and at the time of total gastrectomy in the surviving patient. The authors reviewed 4 similar cases, which had been previously reported. They cited observations by Poth[88] and Elman[89] to support the postulate that an internal secretion of the pancreas may have an influence on ulcer formation. Although peptic ulcer can be caused in laboratory animals by means of sustained insulin-induced hypoglycemia, patients with chronic and severe hypoglycemia resulting from insulin-producing islet-cell tumors of the pancreas generally do not manifest coexistent ulcers. Accordingly, Zollinger and Ellison considered the possibility that glucagon hypersecretion had ulcerogenic effects. Electrophoretic analysis of blood samples of 1 of their patients demonstrated a protein fraction with mobility characteristics similar to those of glucagon. This fraction, which was not present in normal serums, elicited a hyperglycemic response in laboratory animals. Although the patient had certain clinical characteristics suggestive of Cushing's syndrome, there was no evidence either of diabetes or of hyperinsulinism.

Since glucagon administration has been shown by Stunkard et al.[90] to inhibit gastric motility promptly and effectively, it is difficult to believe that it would at the same time stimulate gastric secretion. An opposite effect would be more likely. However, glucagon-induced hyperglycemia is frequently followed by a

period of secondary hypoglycemia during which gastric hypersecretion might well occur. Again, it is difficult to assess the possible long-term effects of a secreting alpha-cell tumor in terms of what is known about the physiologic actions of the short-acting preparation presently available.

### Glycogen-Storage Disease

In glycogen-storage disease glycogenolysis is at fault. At least two types of glycogen-storage disorder exist: in one, the glucose-6-phosphatase activity in the liver is very low; and in the other, structural abnormalities of the hepatic glycogen can be demonstrated.[91,92] Since glucagon acts specifically to increase the concentration of active phosphorylase in the liver, one would not expect this substance to be of therapeutic value in glycogen-storage disease.

The use of glucagon as a diagnostic test in this disease was first described by Van Creveld,[93] who administered an insulin preparation known to contain glucagon as a contaminant to a patient with Gierke's disease and was unable to demonstrate the usual initial hyperglycemic response. Subsequently, purified glucagon preparations were administered to children with glycogen-storage disease by a number of investigators.[94-97] In the first 5 patients who were given glucagon a virtually flat blood glucose curve was observed. This led Schulman and Saturen[94] to suggest that the use of glucagon might have value as a diagnostic test for glycogen-storage disease of the liver. On the other hand, Carson and Koch[97] administered glucagon to 6 patients with "glycogen-storage disease," and the responses were compared with responses to epinephrine administration. Four of the patients failed to show a hyperglycemic response to epinephrine, and 3 failed to have a hyperglycemic response to glucagon. Accordingly, Carson and Koch believe that measurement of the blood glucose changes after administration of glucagon is of little value in the diagnosis of glycogen-storage disease.

Since there are at least several forms of glycogen-storage disease it seems premature to dismiss the glucagon and epinephrine tests as being valueless. The fact that a number of patients with Gierke's disease have failed to respond to glucagon at all is of considerable interest. Such responses must be regarded as being extremely unusual.

It is still possible that the glucagon test will prove to be of value in distinguishing certain forms of glycogen-storage disease, or in assessing the severity of the enzymic defect.

### Glucagon As a Therapeutic Agent and As a Research Tool

Glucagon is harder to place as a clinically useful substance than as a research tool. It may prove to have value as an effective agent for the relief of hypoglycemic states. However, since glucagon-induced hyperglycemia is transient and depends on an adequate supply of liver glycogen, it would be unwise to rely on glucagon alone in the treatment of hypoglycemia. It must be recalled that in normal subjects glucagon-induced hyperglycemia is usually followed by a marked secondary hypoglycemia.

Although glucagon-induced hyperglycemia per se does not seem to be a useful index of liver function, there is evidence that glucagon administered in conjunction with a small dose of epinephrine will produce hyperglycemias that permit a more reliable estimate of liver glycogen content to be made. Whether glucagon-epinephrine hyperglycemia can provide useful information about liver not readily obtainable by means of liver-function tests in current use can be determined only after prolonged and detailed comparative studies. Since an injection of a small amount of epinephrine subcutaneously before glucagon administration accentuates and prolongs the hyperglycemia, such a combination might well be more useful in the treatment of hypoglycemia than either of these substances administered separately.

By means of glucagon administration it is possible to raise blood glucose levels without recourse to intravenous injection of glucose and without the introduction of glucose into the intestinal tract. Therefore, this substance has considerable potential value as a research tool in studies of the physiologic effects of hyperglycemia.

Since Bulatao and Carlson[98] first reported inhibition of gastric motility in fasting dogs by intravenously administered glucose, there has been considerable controversy about the relation between hyperglycemia and satiety. Other investigators were unable to confirm the findings of Bulatao and Carlson, and when, on occasion, intravenously injected glucose did appear to inhibit gastric hunger contractions, the fact that a strongly hypertonic material was being rapidly administered at an "unphysiologic" site (a peripheral vein) made interpretation of the results difficult.[99] In an attempt to obviate these objections, Stunkard, Van Itallie and Reiss[99] studied the effect of glucagon administration on gastric motility in human subjects. They found that glucagon administration was promptly followed by inhibition of gastric hunger contractions and that this effect was entirely reproducible. In their series there was a better correlation between glucose utilization rates (as determined by measuring peripheral arteriovenous glucose differences) and presence or absence of gastric motility than there was between absolute levels of blood glucose and motility.

### Glucagon and Epinephrine

One objection to assigning to glucagon a role in carbohydrate homeostasis has been based on the supposition that it merely duplicates the action of epinephrine and hence is "physiologically superfluous."

Actually, glucagon and epinephrine have quite different actions. Although both substances activate liver phosphorylase and thereby promote hepatic glycogenolysis the resemblance ceases at this point. Epinephrine increases lactic acid production in both liver and muscle.[81] It stimulates muscle glycogenolysis and tends to decrease peripheral glucose utilization.[100-104] Epinephrine also appears to be a weak stimulant of ACTH production by the anterior pituitary gland,[105] and in addition to its many metabolic effects, it has a variety of hemodynamic and autonomic actions.[106] Epinephrine release seems to be at least partly under the control of the hypothalamus, via the splanchnic nerves.[107]

In contrast, when glucagon is administered, blood lactic acid levels do not rise and, indeed, may fall slightly.[81] Muscle glycogenolysis does not occur, and peripheral glucose utilization is not inhibited.[64-67] Glucagon apparently does not stimulate ACTH production, and it has no known hemodynamic effects. Its inhibitory action on gastric motility is probably mediated by the hyperglycemia that it induces.[90]

After epinephrine has been administered the muscles are depleted of glycogen and the respiratory quotient falls.[108] Obviously, then, its role cannot be simply to transfer glucose from the liver to the periphery since its action tends to exclude glucose from the extrahepatic tissues. It may be that, as an emergency mechanism to help combat hypoglycemia, epinephrine acts to ensure that the supply of carbohydrate to the central nervous system is maintained.

## Role of Glucagon in Carbohydrate Homeostasis

Any speculation about the role of glucagon in metabolism must be based on the assumption that it actually is a hormone. Since glucagon raises blood glucose by stimulating hepatic glycogenolysis, it appears that one of its effects may be simply to help maintain blood glucose levels when the blood sugar is falling. There is some experimental support for this view in the previously cited work of Foà and of Sherlock.

Since glucagon apparently does not inhibit and may actually promote peripheral glucose uptake, another of its functions may be to act synergistically with insulin to make glucose available to extrahepatic tissues. Such an action would be particularly useful when the glucose requirements of peripheral tissues are increased, as in muscular activity.

From time to time reports in the literature on carbohydrate metabolism have suggested that after ingestion of food the blood sugar rises more rapidly than can be accounted for by absorption of glucose from the digestive tract.[109] Conceivably, the presence of food in the upper gastrointestinal tract may act as a stimulus for glucagon liberation from the pancreas and subsequent glycogenolysis. In this way the liver would be cleared of some of its glycogen and ready for a new influx of glucose from the small bowel. Increased glucagon secretion may also be a component of the normal satiety mechanism.

The available evidence indicates that the liver has an intrinsic ability to adjust its rate of glucose release to blood glucose changes.[110] Therefore, if glucagon does have any regulatory effect on liver glycogenolysis, such an effect would have to be supererogatory.

## Summary and Conclusions

The medical literature on glucagon has increased steadily since a purified preparation of this material became available to investigators several years ago. Thus, at present, any review of progress in this field must be very much in the nature of an interim report.

On the basis of existing evidence, it is probable that glucagon is a hormone originating in the alpha cells of the pancreas, and that it is involved in carbohydrate homeostasis. Since patients and laboratory animals deprived of their pancreases can function reasonably well with insulin replacement therapy alone, it is clear that the role of glucagon, whatever it may be, is not indispensable. However, it seems significant that insulin sensitivity and susceptibility to ketosis tend to be greater in such depancreatized patients and animals than in other forms of diabetes.

It is generally agreed that glucagon stimulates hepatic glycogenolysis by increasing the concentration of active phosphorylase in liver. As far as is known at present, this is its only primary action.

It has been demonstrated in a number of studies that glucagon is not an insulin antagonist in the sense of interfering with the effect of insulin on the rate of transfer of glucose into cells. Indeed, there is some indication that glucagon administration may actually promote peripheral glucose uptake. Further studies to clarify this point are needed. Other reported metabolic effects of glucagon have not been shown to be independent of its effect on liver glycogenolysis.

Since glucagon raises blood glucose by stimulating hepatic glycogenolysis, its clinical usefulness as a means of estimating liver glycogen content, distinguishing between different types of diabetes, testing liver function and diagnosing glycogen-storage disease is being explored. Glucagon also is being used in studies on the physiologic effects of hyperglycemia, with particular reference to the relation between hyperglycemia and satiety.

Very little work involving chronic administration of glucagon has been reported, and until studies of this kind become available, appreciable gaps in knowledge of the metabolic effects of glucagon will remain. Progress in this direction has been hampered by lack of a suitable long-acting preparation. Moreover, the development of a reliable method for assaying glucagon in blood would be extremely valuable in provid-

ing information about the normal role of glucagon in carbohydrate metabolism.

Important advances in the area of glucagon research may be expected when these two technical problems have been solved.

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# MEDICAL INTELLIGENCE

## THE ARTIST'S TEMPLATE*

### A New Device for Clinical Measurement

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CLINICAL measurement is notoriously inaccurate. Even radiotherapists, a select group of physicians specially trained in the measurement and estimation of tumor shrinkage, are completely inconsistent with themselves and with one another.

A secretary in the Department of Radiotherapy of Bellevue Hospital had a benign nevus on her forearm. Different radiotherapists who attended the clinic were asked to measure the dimensions of this lesion with a standard ruler.

The numerical data produced by these different examiners provided a variable picture of tumor shrinkage and growth. If the measurements were charted according to the day on which they were done, the curve that resulted looked like that of the stock market during a crisis.

An effort to improve clinical measurement resulted in the introduction of the artist's template into clinical medicine (Fig. 1). This is a clear rectangular ruler with a series of holes of increasing diameter bored through it. The diameters in sixty-fourths of an inch are printed over the holes. Artists use it to draw circles of different diameters rapidly.

One can employ the template as a clinical ruler by "ringing" the lesion to be measured. A lesion is "ringed" when all its borders fit into the smallest hole possible on the template.

A repeat experiment with the same lesions and the same examiners showed complete consistency between the measurements of different observers and the same observers at different times.

We believe that inaccurate clinical measurement with an ordinary ruler is due to three factors: the

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measurement of different diameters by different observers; exophytic lesions in which the ruler markings cannot be approximated to the tumor edge; and the difficulty in converting a measurement falling between markings on a ruler into a number.

These difficulties are overcome by the use of the artist's template. All observers now seek the smallest hole into which the lesion will fit. Exophytic growths can protrude directly into the ruler. The possible error introduced by the conversion of ruler markings into a number is eliminated. When one has three holes that roughly approximate a lesion, it becomes

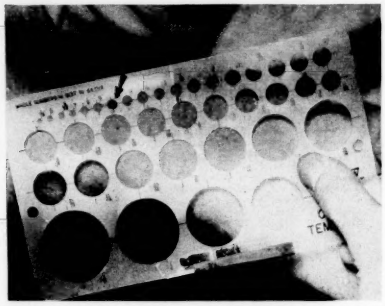

FIGURE 1. *Artist's Template of Clear Plastic, Consisting of Circles of Increasing Diameter Punched out of a Rectangular Form.*

*The whole number over each hole represents its diameter in increments of a sixty-fourth of an inch.*

*The lesion to be measured is fitted into the smallest hole that will completely enclose it; the number over the hole is taken as the diameter of the lesion. One can immediately predict that a lesion has grown when it no longer fits into a hole.*

readily apparent which is larger, which is smaller and which best represents the lesion.

Is improved clinical measurement a nicety of no practical importance? We consider it of value in the following three situations:

If a mole is discovered in a patient undergoing routine physical examination, its dimension should be accurately recorded. If examination at a later date shows interval growth, immediate wide excision should be done. In this manner, early transformation of a benign nevus into a malignant melanoma might be observed before obvious clinical growth has occurred.

We have used the artist's template as a simple, inexpensive tool of experimental radiobiology in the study of skin carcinomas undergoing irradiation. With a patient with multiple skin carcinomas (for example, breast-carcinoma metastases), we have been able to evaluate the response of lesions of different size to different schemes of radiotherapy.

Although we have had no practical experience with such a technic, it seems likely that accurate clinical measurement of the darkened areolae of a woman's breasts might be used as a presumptive test of pregnancy. The physician who has accurate measurements of the areolae at different stages of the menstrual cycle will strongly suspect pregnancy if these measurements are larger than they should be during that period, and especially if they show progressive growth over a two-week period. Considering the frequency with which the physician is faced with determining the presence of early pregnancy in women who cannot afford a Friedman or Ascheim–Zondek test, this should provide him with a useful, inexpensive, accessory clinical tool.

### SUMMARY AND CONCLUSIONS

The artist's template was introduced into clinical medicine to increase the accuracy of clinical measurement. It is a plastic ruler into which holes of increasing, known diameter have been bored. The increased accuracy obtained with it suggests its use in the diagnosis of malignant transformation of a benign nevus, in the study of skin carcinomas undergoing irradiation and as a presumptive test of pregnancy by measurement of the areolae of the female breast.

## BY THE LONDON POST

### Doctors' Remuneration — Hospital Politics — Great Characters

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THE question of the remuneration of the medical profession in the National Health Service was a matter of protracted negotiation at the start of the Service. The terms offered by the Government were based on the recommendations of the Spens Committee, which estimated the total remuneration that the profession could reasonably expect in the light of the previous earnings of general practitioners and consultants. The figures quoted by the Spens Committee were in terms of the 1939 value of money, and since the inception of the Service the only adjustments that have been made have been to bring these figures more nearly into line with the present-day values of money. This adjustment was made by the application of what has been described as the betterment factor. It is now announced that physicians are to seek an actual increase in their remuneration. The announcement was made in a joint statement by the leader of the consultants of the country, Sir Russell Brain, P.R.C.P., and Dr. Talbot Rogers, the representative of the general practitioners.

It is pointed out that when Parliament introduced a state-provided health service it assumed the responsibility of maintaining an adequate standard of living

for the doctors taking part. Since 1950 there has been a steep rise in the cost of living and a fall in the purchasing power of money, but during this time the medical profession has sought for no increase in pay. It is certainly unfortunate that the present claims for more pay should have come at a time when the economic state of the country makes it essential that there should be restraint in wage demands of all kinds. Indeed, there has been a brisk correspondence on the subject in both the national and the medical press. Some writers have suggested that no claims for increased pay should be made at present, and a motion to this effect was passed by a meeting of the fellows of the Royal College of Physicians of Edinburgh. On the other hand, other writers have stressed that it is usually the more senior and more successful members of the profession who have suggested that the claim should not be pressed. Many of these men are still fortunate in having considerable incomes from private practice and are out of touch with the problems of the younger men, who are often entirely dependent on the income they derive from their work in the National Health Service. One correspondent has said "that the professional classes should lead and not follow the crowd" in the matter of increased remunerations. This is a fine thought, but it is undoubtedly true that there are many members of the profession who are carrying financial burdens; it is only right that their claims should be put forward, and they will have little chance of success if any disunity in the profession is apparent.

* * *

In all spheres of public and professional life it is well known that politics play a part. Hospitals have always been well known for the part that influence may have played in a man's success in attaining staff rank. Influential relatives, working for the right chief, being neither too brilliant nor too stupid — these have all been important factors in success, and the cynics have often remarked that "who you know is more important than what you know."

One of the aims of those who set up the conditions and terms of service in the National Health Service was that all such influence should be eliminated and that in all appointments the only criterion should be that the best man should get the job. To this end, the appointment of senior hospital staff was removed from the hands of the local staff and carried out by an independent committee. Only 2 members of the committee come from the local hospital, the remaining 4 being nominated by a remote regional hospital board. It is no secret that there are grave doubts in the minds of many who serve on the committees, and by even more men who appear before them, whether the new system is any less evil than the old. Although canvassing by the candidate is strictly forbidden and disqualifies him from the contest there is no way of preventing indirect canvassing on his behalf. Indeed, his sponsors and referees might think it only right and proper that they should acquaint any member of the committee with the full facts regarding the man's merits. It is easy to see, however, how conflicting interests could arise and how the technics around the conference table could wander away from the prime object of appointing the best man.

The kind of situation that may arise has been depicted in a recent novel, *The Pack*, which records the fortunes and misfortunes of a young surgeon struggling to establish himself. The young surgeon, being himself the supposed author of the novel, describes his experiences in applying for junior posts. He is frank in admitting that his appointment was greatly influenced by the wish of the senior staff to displace another junior, the jealousy between two of the senior surgeons and, most important of all, by his own proposal of marriage to the daughter of the most influential man. From this experience and others he concludes with consternation that doctors become insensitive to scruples as soon as they go into committee, whether to appoint a staff member or to inquire into an unexplained hospital death. His greatest dismay comes from his cynical observation that they mostly arrive at an unjust conclusion while remaining thoroughly well meaning to the outside observer.

Although it is admitted that exaggeration has helped in the writing of the novel it would be idle to pretend that there is no more than a grain of real truth in many of the fictitious suggestions. It is, of course, equally true that hospital life is only one setting for the revelation of such failings of human nature.

* * *

Every medical school has its great characters. Some seem to be so identified with the place that when one reads that one of them has died it is hard to grasp because one has come to think of them as almost immortal.

One such character in the Cambridge Medical School was Dr. Wynfrid Duckworth. For more than sixty years he taught anatomy at Cambridge as demonstrator, lecturer and reader, in which time thousands of students passed through his hands. From each one he drew unqualified admiration, devotion and affection. He was not only a superb teacher whose enthusiasm for anatomy was infectious but also one of the most courteous gentlemen one could ever wish to meet. His tall, dignified figure bending over a dissection must be a memory familiar to many undergraduates. To those who were finding the dissection too much, his appearance on the scene was always a relief because in a moment, he could restore order from chaos, remarking in an inimitable way "and here gentlemen, or hereabouts we should expect to find and indeed we do find — the vagus nerve." His blackboard drawings were so legendary that a classical student is reputed to have explained his

presence at an anatomy lecture by saying he had come "to see Duckworth draw."

But his influence extended far beyond the Cambridge Anatomy School. In 1903 he took part in an expedition to the Mediterranean to obtain anthropologic data on the ancient and modern inhabitants of Greece, and he later earned an international reputation as a comparative anatomist. He served his own college, Jesus College, as master during World War II, and when he was not elected to the chair of anatomy, a position in which the whole student population over many years would have hailed him with unanimous acclamation, he neither murmured nor wavered in his loyalties.

Few men can have given longer service more humbly, and few can have had a greater influence for good over such a large number of students. With his death at the grand age of eighty-five, "Ducker" of the Cambridge Medical School becomes a legend.

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# CASE RECORDS
## OF THE
## MASSACHUSETTS GENERAL HOSPITAL

### Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

## CASE 42171

### PRESENTATION OF CASE

A fifty-five-year-old woman was brought to the hospital after being found unconscious.

Four years previously she sustained a fracture of the mandible. At that time the blood pressure was 210 systolic, 120 diastolic, and the heart was slightly enlarged to the left. Five months before admission she was seen in the Out Patient Department because of dyspnea on exertion. At this time the blood pressure was 180 systolic, 100 diastolic, in both arms and 200 systolic, 110 diastolic, in the right leg. A few inspiratory rales were heard over the left lung. The heart was again noted to be enlarged. The aortic second sound was louder than the pulmonic. Grade 2 aortic systolic, Grade 1 aortic diastolic, and Grade 3 apical systolic murmurs were audible. Neurologic examination was negative. An electrocardiogram showed a normal sinus rhythm, a rate of 100 and high voltage over the chest leads, with ST-segment and T-wave depression. X-ray films of the chest showed some fibrosis in both lung fields, left ventricular enlargement and a tortuous aorta with calcification in the arch anteriorly. With digitalis therapy the exertional dyspnea decreased, and she was able to return to work. She remained well until the episode of unconsciousness on the day of admission.

On admission to the Emergency Ward physical examination revealed a slight, thin, acutely ill woman who was responsive but confused. The fingers were cyanotic and cold — more so on the left side than on the right. The legs were at first equally pale, but when the feet were elevated the right leg became paler than the left. No pulsations were palpable in the left upper and right lower extremities. Fine, moist rales were present at both lung bases. The chest was moderately emphysematous. The point of maximal cardiac impulse was at the left anterior axillary line. Aortic systolic and diastolic murmurs and apical systolic murmurs were present as previously noted. There was a regular sinus rhythm. The liver edge was percussed 3 cm. below the right costal margin. The abdomen was normal. The pupils were equal and reactive. The fundi were poorly visualized because of cataracts. There was a questionable homonymous hemianopsia on the right. The patient was unable to move the right upper extremity and the distal portion of the left upper extremity. Sensation to pinprick was impaired in the pulseless extremities. Deep tendon reflexes were symmetrically equal.

The temperature was 98°F., the pulse 50, and the respirations 28. The blood pressure was 100 systolic, 70 diastolic, in the right arm and 140 systolic, 0 diastolic, in the left leg; it was not obtainable in the left arm and right leg.

While awaiting transfer to the ward, the patient had two sudden episodes of vomiting associated with dyspnea, fecal incontinence and Cheyne–Stokes breathing. The apical pulse was noted to be regular, and she did not complain of pain. During one of these episodes she fell to the floor and sustained a laceration of the right occipital region and upper lip. After this she tended to doze off when no one spoke to her.

Urinalysis revealed a + + test for albumin, 5 to 8 white cells and 3 to 4 granular casts per high-power field in the sediment and a green test for sugar. Examination of the blood revealed a hemoglobin of 13 gm. per 100 ml. and a white-cell count of 22,200, with 90 per cent neutrophils. The fasting blood sugar, while 5 per cent dextrose was being administered intravenously, was 176 mg. per 100 ml. The nonprotein nitrogen was 28 mg. per 100 ml., and the serum sodium 131 milliequiv., the chloride 100 milliequiv.,

and the potassium 4 milliequiv. per liter. Stool and vomitus were negative for occult blood. An electrocardiogram showed a normal sinus rhythm, with regularly recurring ventricular ectopic beats producing bigeminy. The ST segments were markedly depressed in Leads 2, 3 and aVF and slurred in Leads 1, aVL and $V_4$ through $V_6$. Throat culture grew out abundant alpha-hemolytic and a few nonhemolytic streptococci. Blood and urine cultures were negative. Roentgenograms of the skull were normal. X-ray films of the chest showed an enlarged heart and a tortuous aorta.

Upon arriving on the ward, the patient was alternately somnolent and quite alert. Respirations continued to be of Cheyne–Stokes type. She was bleeding actively from both nostrils, and red blood coated the tongue. Grade 2, diastolic, aortic and Grade 2, systolic, aortic and Grade 3, systolic, apical murmurs were now heard. She seemed to move all extremities; however, there was considerable generalized weakness, which was most marked in the right arm. The reflexes were now normal and bilaterally equal. Sensory evaluation was difficult, but sensation was thought to be normal. Physical examination was otherwise unchanged. She continued to vomit small amounts on several occasions, but she was able to speak and took fluids well; 900 mg. of Tromexan and 300 mg. of Dicumarol were given by mouth. Four hours after arrival on the ward the pulse became palpable in the left radial artery. Two hours later she died suddenly.

## Differential Diagnosis

Dr. Robert S. Palmer*: This patient presents the same problem as many middle-aged and elderly patients who are brought to the Emergency Ward unconscious or nearly so. In the differential diagnosis, the familiar possibilities to consider are intoxication, trauma, overwhelming infection, metabolic emergencies such as diabetic coma and adrenal failure and cardiovascular accidents. In treating the patient who can give no history the physician, like the horse doctor, must depend on objective signs.

May I see the x-ray films? I should like to ask particularly whether or not the aorta had changed in size and shape. Was there any irregularity of its border or flattening of the knob? Were there any of the changes that might be seen with a dissecting aneurysm?

Dr. Richard V. Wilson: I cannot see those changes in these films.

Dr. Palmer: Will you describe the changes you would expect with a dissecting aneurysm?

Dr. Wilson: The aorta is larger than normal; if there are earlier films of the same patient for comparison, the aorta may be larger than previously. The border is frequently hazy or obliterated. In this patient we have two sets of films taken four months apart; in both sets the aorta looks about the same. In the later film I do not see the entire outline of the aorta, but the portion that is most frequently involved in a dissection is clearly visible and does not suggest a dissection. Sometimes, there is calcification in the aorta; when the aorta is visible beyond the calcification, that is suggestive of a dissecting aneurysm. I do not see that here. It is stated in the protocol that there was calcification in the ascending aorta, such as we see with syphilitic aortitis; however, calcification is also present in the descending aorta so that I do not think it means anything. The size of the heart in the last examination is the same as on the one four months previously; the left ventricle is quite large. On fluoroscopy, there was no evidence of enlargement of any other chamber. There is calcification of the annulus fibrosus of the mitral valve, but none in the valve itself.

Dr. Palmer: Can you see any calcification in the region of the aortic valve?

Dr. Wilson: I do not think that there is any calcification in the aortic valve, but I cannot be sure.

There is some fibrosis in the lungs. The films of the skull were not taken in true positions. I cannot see the pineal gland on the single anteroposterior film. There is calcification in the internal carotid arteries. The posterior clinoid processes are poorly shown in these projections. I think that is an indication of the poor quality of the films rather than of increased intracranial pressure. I see nothing else of significance.

Dr. Palmer: I know that this patient had generalized arteriosclerosis, with hypertension and calcification of the aorta, as well as disease of the aortic valve, with regurgitation and possibly dilatation of the mitral ring or mitral regurgitation. She may have had rheumatic valvular disease although the typical findings of combined mitral-valve and aortic-valve disease were not present. She may have had syphilitic heart disease even though "free" aortic regurgitation was not indicated by the physical signs or the levels of the blood pressure. I do not know what the serologic test may have shown.

This patient had the background for and, on admission, some findings suggesting aortic dissection, which may have affected the ostia of the great vessels and the right iliac artery. The findings that support this diagnosis are the changes in consciousness without neurologic localization; variable weakness in the right arm, possibly with impaired sensation but without pain; and the evidence of "spotty" or variable ischemia in the extremities. She had no pain peripherally or in the region of the chest to which pain from the heart is referred. Impaired sensorium and near coma may have prevented the sensation of pain that we are questioning. All I can say is that I have not yet encountered a patient with a dissection of the aorta in whom there was no history of a sudden, tearing pain. I am aware that the so-called neurologic type of aortic dissection has been reported, and I suppose that it must occur. Dr. Wilson has films taken

*Physician, Massachusetts General Hospital.

four months before and on admission and can see no change in the aorta in that interval. In the absence of a history of tearing pain, even though the patient's condition precludes subjective symptoms and suggests that aortic dissection itself may have impaired the sensorium, I cannot bring myself to make this diagnosis without objective evidence.

The ST segments in the electrocardiogram were depressed or slurred, I think, and evidently the physicians caring for the patient thought that this was the result of digitalis. May I look at the electrocardiograms?

DR. BENJAMIN CASTLEMAN: We do not have them here; we have only the last one.

DR. PALMER: The depression of the ST segments may have been the result of digitalis or of myocardial ischemia.

DR. CASTLEMAN: It was interpreted as the effect of digitalis.

DR. PALMER: The patient may have been given more digitalis than she needed, which may explain the slow pulse and the vomiting. I shall take this interpretation seriously. Perhaps the digitalis effect covered up the pattern of myocardial ischemia in the electrocardiogram. She had generalized arteriosclerosis so that she may have had a myocardial infarction, with a fall in blood pressure and spontaneous thromboses in the peripheral arterial circulation. I have never seen this occur although I have seen the opposite — that is, a fall in blood pressure that produced coronary thrombosis with myocardial infarction. She may have had myocardial infarction with a mural thrombus, from which emboli broke off. In a high percentage of cases of myocardial infarction, up to 30 per cent, there are mural thrombi with embolization. Since this was an acute process, it was early for peripheral emboli from a myocardial infarction; therefore, I do not accept this possibility.

Could peripheral emboli have come from subacute bacterial endocarditis? There were no petechiae and no history or background to suggest subacute bacterial endocarditis. The patient may have been sick previously and may have had an embolus to the brain, with impairment of the sensorium. She may have had successive emboli while she was in the hospital, but this does not seem likely to me.

The changing states of consciousness are interesting, occurring with infection, as in meningitis and in sinus thrombosis, but I have no reason to think that she had any of these. I wonder if this picture may have been the result of recurring variable cerebral ischemia from occlusion of the carotid artery or by pressure upon it, from changes in the cardiac output, as in aortic stenosis, or from changes in position of an intracardiac ball thrombus. There was no good evidence of aortic stenosis. There was no considerable enlargement of the left atrium and no evidence of a tight mitral stenosis or anything to indicate ball thrombus in the heart. Nor do I see any reason to believe that the patient had an intracardiac tumor or any of the rare conditions that might have acted like a ball-valve occlusion of the mitral opening.

The slow pulse, the vomiting, the loose stools and the impaired sensorium could not all be explained by digitalis, but the ventricular extrasystoles, with the bigeminy, suggest that she may have had a toxic dose of digitalis, which may have contributed to the disordered cardiac rhythm and to the death. In this case no specific cause of death may have been found at autopsy other than changes that had been present for a long time.

Another possibility is that she may have received Rauwolfia. Could *Rauwolfia serpentina* have slowed the pulse, caused vomiting and diarrhea, all of which it does, and lowered the blood pressure sufficiently so that she was subject to peripheral thromboses? Patients in mental institutions have received huge doses of Rauwolfia, but I have not yet heard of 1 who suffered a hypotensive state sufficient to cause peripheral thromboses.

I assume that I have been given all the relevant data. I must admit that I do not have the wit to choose accurately among the possibilities I have mentioned or to think of better ones.

DR. CASTLEMAN: Should you like to put one at the top of the list?

DR. PALMER: I suppose one should try to make the diagnosis since it makes no difference to this patient, but I also believe that it is proper not to make a diagnosis if one can show good reasons why a diagnosis cannot be made on the available data: in this case the absence of a key point in the history and the lack of a specific objective sign — namely, x-ray changes in the aorta; I honestly think that I have done that.

DR. CASTLEMAN: Dr. Clark, will you take Dr. Palmer's list and choose a diagnosis?

DR. RICHARD J. CLARK: It seems to me that Dr. Palmer has mentioned all the possibilities that anyone could consider. I think that I should put dissecting aneurysm at the top of the list. The only two conditions of which I can think that would suddenly cause these various circulatory obstructions are multiple emboli from some source and dissecting aneurysm.

DR. PALMER: As a probability, but do you not think that the patient should have had changes in the aorta and acute tearing pain at the beginning for that diagnosis to be made? I do.

DR. CLARK: I gather that she was unconscious on admission; she may well have had an acute, tearing pain before she was seen. I do not believe that her mind was ever clear when she was here.

DR. PALMER: In the reports of 125 ante-mortem diagnoses of dissecting aneurysm that I have been over, neurologic types have been described, but I could not find out whether or not the patients did have pain. It is not our business to supply a patient with a history simply because she cannot give one.

DR. CLARK: You never explained the blood that came from the nose.

DR. PALMER: She had fallen on the floor. By the way, if dissecting aneurysm was the leading diagnostic choice and in addition she was bleeding freely from the nose, why did the house staff give her such a generous dose of anticoagulant?

DR. CLARK: I wondered about that also.

DR. WARREN POINT: Could she possibly have had digitalis intoxication, leading to arrhythmias and temporary lowering of blood pressure and resulting in a fall at home, during which she sustained a subdural hematoma?

DR. PALMER: I intended to mention subdural hematoma. The eye grounds could not be seen and a lumbar puncture was not done, even though she had signs of central-nervous-system involvement, with the vomiting and slow pulse. I cannot make the diagnosis although it is a possibility. She may have had digitalis intoxication, as I said, and ventricular arrhythmia, as you suggest, and may have died of ventricular fibrillation and standstill, with changes at autopsy no different from those that she may have had for some time.

DR. CASTLEMAN: Dr. Palmer, the diagnoses on discharge were cardiac arrhythmia, paroxysmal; hypertensive heart disease; calcific aortic stenosis; Cheyne–Stokes respirations; and peripheral embolization.

DR. PALMER: There must have been other electrocardiograms; in all reported here the rhythm was normal.

### CLINICAL DIAGNOSES

Cardiac arrhythmia, paroxysmal.
Hypertensive heart disease.
Calcific aortic stenosis.
Peripheral embolization.

### DR. ROBERT S. PALMER'S DIAGNOSIS

(Insufficient evidence on which to make positive diagnosis.)

### ANATOMICAL DIAGNOSIS

*Dissecting aneurysm of aorta.*

### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The brain showed some atrophy and a great deal of arteriosclerosis on gross examination, but there was no subdural hematoma.

The heart was somewhat hypertrophied, especially the left ventricle. In the ascending aorta just above the aortic valve was a very large tear in the intima, which had resulted in a dissecting aneurysm (Fig. 1). The dissecting channel surrounded the mouths of both coronary arteries. That happens not infrequently and may give rise to anginal pain and on rare occasions to myocardial infarction. The gross examination and the microscopical sections of the myocardium, however, showed no infarction. This dissection within the media involved the mouths of all three branches of the aorta at the arch and extended for a short distance into each. The internal carotid artery in the brain was not involved. The dissection extended into the mouths of both renal arteries, but apparently had not compromised the kidneys sufficiently to produce anuria or hematuria. It involved the iliac arteries,

FIGURE 1. *Photograph of Heart and Aorta.*
*The upper arrow points to the intimal tear, and the lower arrow to a medial hematoma in the iliac artery. The descending aorta shows the opened dissecting aneurysm with the original aortic lumen unopened.*

and cross-section of one of the iliac arteries demonstrated a blood clot in the media that had resulted in a bulge of the intima into the lumen (Fig. 1). This bulge can occur in any of the branches of the aorta to cause a temporary ischemia, which I believe may have occurred in the brain to produce the fall. I think that Dr. Clark may be correct: the patient may have had a tearing pain before she was found unconscious. We have no idea how long she had been unconscious on the floor.

The cerebral manifestation of dissecting aneurysm was reviewed some years ago by Dr. Adams* when he was at the City Hospital; perhaps he can tell us a little about it.

*Weisman, A. D., and Adams, R. D. Neurological complications of dissecting aortic aneurysm. *Brain* **67**:69-92, 1944.

DR. RAYMOND D. ADAMS: In looking over the pathological material of a large series of cases of dissecting aneurysms, I was impressed with how frequently neurologic symptoms had occurred. Moreover, it was evident that the recognition of neurologic symptoms and their proper interpretation may at times be helpful in the diagnosis of dissecting aortic aneurysm. There were 3 common syndromes that appeared in over 30 cases on which I had seen the post-mortem material. The most frequent was paralysis of a single limb, with a distal paralysis and sensory loss — an ischemic neuropathy. This was invariably indicated by a lack of pulse in that limb. When one sees such paralysis with sensory loss combined with tearing pain or other signs of some catastrophe in the chest, the first consideration should be dissecting aortic aneurysm and a blockage of the main circulation to the limb. Extensive dissection of the thoracic and abdominal aorta often produced a second syndrome — namely, an ischemic necrosis of the spinal cord as a result of interference with the circulation of the spinal cord. This is especially likely to occur with a dissection that involves many intercostal arteries, and along with it other symptoms of visceral disorder, a paraplegia with a sensory and motor level on the trunk, and paralysis of the bladder and bowel become manifest.

DR. CASTLEMAN: That would be the anterior spinal artery?

DR. ADAMS: Yes; the ischemic necrosis is in the anterior portion of the spinal cord, which is fed by numerous collateral vessels that contribute to the anterior spinal artery.

The third syndrome, which is quite infrequent and in which there may be puzzling clinical states, is interference with the circulation to the brain. This may happen suddenly as the first symptom of aneurysm, and owing to loss of consciousness the patient is unable to feel the pain in the chest or to report it to the physician. Here, one or both of the carotid arteries are blocked by the dissection. In addition to coma there may be hemiplegia or aphasia. I thought that that might have been the case here although now that I know the pathological findings I think that the circulatory collapse probably resulted in general ischemia of the brain because there was no interference with the carotid or vertebral circulation.

DR. CASTLEMAN: There was dissection of the carotid artery for a short distance.

DR. ADAMS: I understood that the lumen was patent.

DR. CASTLEMAN: At the arch there was some dissection; the degree of patency, I think, is difficult to ascertain at the time of post-mortem examination.

DR. ADAMS: Which side?

DR. CASTLEMAN: The left common carotid artery.

DR. ADAMS: So that some of the vague right-sided signs may have been caused by a temporary ischemia of the left side of the brain.

DR. PALMER: The patient had atrophy that must have been present for some time.

DR. CASTLEMAN: It is interesting that there was no external rupture of the dissection to produce a hemopericardium or hemothorax such as is often seen.

DR. ADAMS: There was then blockage of the vessel to the left arm and right leg and left carotid artery.

DR. ARTHUR S. PIER, JR.: Why did the pulses return after a time?

DR. CASTLEMAN: I think there may have been a temporary block and later enough blood passed into the main circulation to push the dissection to one side.

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## CASE 42172

### PRESENTATION OF CASE

A twenty-nine-year-old woman entered the hospital because of poliomyelitis.

Four days previously she had a sore throat. The next day persistent stiffness of the neck was noted. The day before entry she had a throbbing headache, and she felt febrile and slept poorly.

Physical examination was negative except for marked stiffness of the neck.

The temperature was 100.6°F. by rectum, the pulse 108, and the respirations 12. The blood pressure was 106 systolic, 78 diastolic.

Examination of the blood revealed a hemoglobin of 14 gm. per 100 ml. and a white-cell count of 11,500. The urine was normal, as was an x-ray film of the chest. Culture of the throat grew out abundant alpha-hemolytic streptococci. On lumbar puncture 6 ml. of slightly turbid cerebrospinal fluid under an initial pressure equivalent to 114 mm. and a final pressure equivalent to 84 mm. of water was obtained; the cell-count was 260, with 80 per cent lymphocytes and 20 per cent neutrophils, the Pandy test + + +, and the sugar 70 mg., and the protein 184 mg. per 100 ml.; culture showed no growth.

On the first hospital day the patient had an episode of diplopia, and there was slight weakness of left lateral gaze. By the next day she had to be placed in a respirator because of rapid, shallow respirations, with dyspnea. The intercostal muscles were used in breathing, and there was difficulty in swallowing, the voice was weak, with a nasal quality; there was diplopia to right lateral gaze. A right-sided facial weakness was present, and there was a left-eleventh-cranial-nerve palsy and marked weakness of both deltoid muscles as well as other muscle groups in all extremities, and she was unable to void. The vital capacity was 150 ml. Two days later quadriplegia was noted, and, because of accumulated tracheobronchial

secretion and limitation in movement of the palate, a tracheotomy was performed.

On the fifth hospital day there were two episodes of "air hunger," with cyanosis and a rise in the blood pressure to 160 systolic. Bronchoscopic examination showed a clear airway. With positive and negative pressure oxygen and superinone administered intermittently with an aerosol nebulizer the patient's color improved, and the blood pressure and pulse stabilized at normal levels. The tidal air volume was 150 to 175 ml. Urinalysis revealed a + test for albumin; the sediment contained 50 red cells, 5 white cells and numerous bacteria per high-power field; culture grew out abundant *Proteus vulgaris* and moderate coliform bacilli. Streptomycin therapy was given for five days, during which the temperature ranged between 99 and 101°F. On the eighth hospital day, because of obstruction of the trachea, bronchoscopy was performed, and a fibrin-mucous plug measuring 4 cm. in length was removed from the trachea. Tracheal culture grew out abundant *Staphylococcus aureus* and alpha-hemolytic streptococci and a few *Haemophilus influenzae*. On the next day large, encrusted secretions and blood clots were removed at bronchoscopy, with improvement in the tidal air volume to between 300 and 450 ml. Despite constant superinone, tracheal humidification and potassium iodide, mucous plugs continued to form in the trachea and main-stem bronchi, requiring almost daily bronchoscopies. On the thirteenth hospital day there was a rise in the blood pressure to 150 systolic, with cyanosis, dyspnea, tachycardia (a rate of 140) and a temperature rise to 104.4°F. Several bronchoscopies with tracheal suction were necessary before considerable mucus was removed from the left main bronchus with improvement. The urine was normal. Examination of the chest on the next day showed well aerated lungs, with some rhonchi heard posteriorly. There was an episode during which the patient appeared cyanotic, stared off into space and responded only to pain by grimacing. Vigorous tracheal suction dislodged three small mucous plugs. The serum carbon dioxide was 22 milliequiv., and the oxygen 15.2 milliequiv. per liter. The arterial oxygen saturation was 96 per cent, the oxygen capacity 14.2 vol. per cent, and the serum pH 7.4. An electrocardiogram showed a sinus tachycardia at a rate of 150; the PR and QRS intervals were 0.14 and 0.08 second, respectively; there was a tendency to low voltage. In spite of aminophylline and hydrocortisone therapy, there were periodic episodes of diminished oxygenation and tidal air volume, which were relieved by bag breathing or bronchoscopic aspiration. Thick, viscous tracheobronchial secretion containing some blood continued to be formed. There was some improvement in palatal movement, and by the twenty-fourth hospital day the patient was able to void but the quadriplegia persisted. The serum electrolytes remained within normal limits.

She continued to be febrile, with a temperature rise to 104.6°F. on the fourteenth hospital day; thereafter, the temperature ranged between 99 and 102.4°F., with a spike to 104°F. on the thirtieth hospital day. Erythromycin and Chloromycetin were given during the next ten days, and bacitracin for a week. On the twenty-seventh hospital day a blood culture grew out *P. vulgaris*, which showed only fair sensitivity to Chloromycetin and neomycin. Tracheal cultures during this time continued to grow abundant *Staph. aureus*, which showed only fair sensitivity to Chloromycetin and bacitracin and was not sensitive to penicillin, streptomycin, erythromycin, Terramycin, Aureomycin or Achromycin. Urine culture on the twenty-ninth hospital day grew out abundant coliform bacilli, which showed good sensitivity to all antibiotics except streptomycin. The white-cell count ranged between 9400 and 21,700. A diffuse papulopustular skin rash, which subsequently subsided, was noted over the upper part of the body on the eighteenth hospital day. Because of a gradual fall in the hemoglobin, which was 10.9 gm. per 100 ml. on the twenty-second hospital day, the patient was given 500 ml. of whole blood and iron therapy. On the twenty-seventh hospital day there was an episode of hypotension. An electrocardiogram showed a sinus tachycardia at a rate of 140; the PR and QRS intervals were 0.12 and 0.06 second, respectively; the T waves were upright in the standard leads, aVL, aVF and $V_2$ through $V_6$; there was a normal RS progression in the precordial leads. She continued to have recurring episodes of hypotension.

On the twenty-seventh hospital day she was given 50 mg. of Thorazine intramuscularly. Two days later jaundice was noted. Examination of the chest was negative. There was tenderness of the right calf. The liver edge, which was nontender, was palpable 1 fingerbreadth below the right costal margin. Examination of the blood revealed a hemoglobin of 10.9 gm. per 100 ml. The serum bilirubin was 6.6 mg. direct and 9 mg. per 100 ml. total. The alkaline phosphatase was 10.6 units. The serum cholinesterase activity was 0.33 delta pH per hour, and the transaminase was 120 units. The Coombs test was negative. The cold-agglutinin titer was 1:2. Culture of the trachea again grew out *Staph. aureus* and a blood culture grew out *P. vulgaris*. Chloromycetin and streptomycin were given in addition to bacitracin. On the thirty-second hospital day tenderness of the left calf and edema of the right thigh and leg were noted. An erythematous skin rash attributed to drug sensitivity was noted. Slight jaundice, which later subsided, was still present. The liver edge was tender and palpable 2 fingerbreadths below the right costal margin. The white-cell count was 17,100, with 89 per cent neutrophils. With cessation of antibiotic therapy the temperature rose to 102.6°F. Neomycin therapy was begun on the thirty-sixth hospital day. There was an episode of painful swelling of the left parotid gland; culture of Stensen's duct grew out

abundant alpha-hemolytic streptococci and a few coliform bacilli and *Staph. aureus*. On the forty-sixth hospital day, after twelve days of neomycin therapy, the temperature was 102.4°F., and the white-cell count was 17,700, with 97 per cent neutrophils. Blood cultures were negative. Antibiotic therapy was stopped. The temperature subsequently ranged between normal and 100.6°F.

On the forty-ninth hospital day there was slight cyanosis and marked dyspnea. Attempts at suctioning were unsuccessful. A catheter was passed with great difficulty and did not enter either bronchus. With vacuum clearing the patient experienced subjective relief, but the tidal volume was only 300 ml. Exsufflation with a cough machine produced deep cyanosis, and suctioning was still nonproductive. Because of marked tracheostenosis an adult bronchoscope could not be passed as far as the carina. With an infant-sized bronchoscope a moderate amount of mucus was aspirated from the right main bronchus; the orifice of the left main bronchus was too small to permit passage of the bronchoscope. After bronchoscopy a considerable quantity of bloody mucus was aspirated from the trachea; the tidal volume was 425 ml., and the patient felt much relieved. Obstruction at the carina persisted. The airway was maintained with warm humidified air and suctioning with hard-tipped catheters; increasing negative tank pressure to the level of −30 cm. of water was required. Examination of the chest on the fifty-sixth hospital day was negative. The swelling and tenderness of the right leg subsided, and the skin rash disappeared. By the sixtieth hospital day, because of increasing difficulty in maintaining the tidal air volume above 300 ml., bronchoscopy was again performed, and an increase in the stenosis was seen. The white-cell count was 19,500. The arterial oxygen saturation was 100 per cent. The serum carbon dioxide was 29 milliequiv. per liter, and the pH was 7.41. An x-ray film of the chest was normal. Neomycin was resumed on the sixty-second hospital day. Bronchoscopy on the sixty-third hospital day showed concentric narrowing of the distal trachea, with obliteration of landmarks; the mucosa appeared diffusely injected and edematous and bled easily; culture of the tracheal aspirate grew out moderate *Staph. aureus* and rare nonhemolytic streptococci. With frequent suctioning the tidal air volume was maintained at about 350 ml. Except for diffuse, soft rhonchi, examination of the chest was negative. Because of a rise in temperature to 102°F. on the sixty-sixth hospital day penicillin therapy was begun. On the seventy-eighth hospital day the patient again became cyanotic and required tracheal suction and bag breathing. The tidal air volume averaged 250 ml. In spite of positive and negative pressure oxygen, frequent tracheal suction, bag breathing and vaporized hydrocortisone, progressive tracheobronchial obstruction developed. She became unconscious and died the next day. During the last week of life the temperature was normal.

## Differential Diagnosis

Dr. William Berenberg*: Obviously, the diagnosis of bulbospinal poliomyelitis was clear, and for about seventy days this patient received heroic, dedicated and continuous care. I do not, therefore, need to discuss a differential diagnosis of the basic disease. On admission, the respiratory rate was 12, and the temperature 100.6°F., which means that she was "in trouble" at that time. I do not believe that the change on the second day was as dramatic or unexpected as the protocol indicates. The cranial-nerve palsy noted on the first day also suggests bulbar palsy at that time. The first determination of vital capacity revealed a striking diminution to 150 ml., the anticipated normal being 3 to 3.5 liters. The vital capacity in a febrile patient with respirations of only 12 and cranial-nerve palsy should be carefully watched during the first twenty-four hours. Because of this, she might well have been placed in the respirator sooner, although the clinical course might have been the same.

I shall not discuss all the points because we should be here several hours, but will select those that merit special discussion. On the fifth hospital day the patient became cyanotic and hypertensive. The elevated blood pressure may have been related to central-nervous-system damage or to respiratory obstruction, with increasing amounts of carbon dioxide in the blood. The tidal volume of 150 ml. certainly means that this woman was severely hypoxic and in spite of every effort to improve the oxygen intake, she had multiple recurrent episodes of severe hypoxia throughout the hospital course.

The hematuria noted on the fifth day, I am sure, meant hemorrhagic cystitis, which is common in patients with poliomyelitis who have been catheterized for four or five days.

Was the patient admitted during the last epidemic?

Dr. Benjamin Castleman: Yes, in the summer of 1955.

Dr. Berenberg: When hematuria occurs in a patient with poliomyelitis, one always considers renal calculus, for calcium may be mobilized in quadriplegic patients who have been completely immobile for long periods. The patient under discussion, however, had been ill for only ten days; therefore, I think that infection as evidenced by bacteria in the urine is a more likely explanation for the hematuria.

On the eighth day the tracheal plugs, which I think were the beginning of the end, appeared. At bronchoscopy a large plug was removed, culture of which revealed *Staph. aureus*. The plug and infection heralded major difficulty.

It is difficult to know how to evaluate the effect of the multiple bronchoscopies. It is easy to say that one should never bronchoscope a patient as often as several times a day; it is difficult, when one is confronted with a patient about to suffocate, to withhold bron-

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choscopy. Certainly, even in the most capable hands, bronchoscopy of an acutely ill patient with respiratory difficulty may cause trauma. With repeated bronchoscopies under emergency circumstances the chances for trauma are increased. The story of repeated bleeding from the bronchus after bronchoscopy may also support the possibility that the multiple bronchoscopies were traumatic. The *Staph. aureus* is a disturbing organism in the tracheal tree. Many patients with repeated plugging of the trachea whom I have seen in recent years have had *Staph. aureus* infections. One patient with Tridione sensitivity producing inflammatory reaction had a secondary *Staph. aureus* infection. His trachea was denuded of its mucosa and epithelium, and the stenosis could not be controlled. I think the *Staph. aureus* infection itself is as important here as the mechanical factor. In retrospect one could say that in view of this infection, this patient perhaps should have received Chloromycetin, to which the organism was sensitive, immediately after the original cultures were reported. She was on Chloromycetin for only six days; that may have been one reason why the organism persisted.

The many topical agents that were used, I agree, were worth trying; certainly none of them were particularly harmful. The question of the use of proteolytic enzymes always arises in this type of situation. I am afraid of these on the basis of personal experience, although trypton has been used successfully in other places. The most important mechanical treatment is adequate humidification. In the years before good humidification was practicable, patients with tracheobronchial inflammation presented a monotonous picture of repeated bronchoscopies for multiple plugs and concretions. I do not know what technic of humidification was used in the patient under discussion, but with any good technic I should have expected much less difficulty than she had. Infection was certainly the next great bugaboo in this case. All of us who dealt with many patients with poliomyelitis under very difficult circumstances this past summer knew many times that we were in serious trouble from this point of view. I think *Staph. aureus* and *P. vulgaris* could be cultured from the floors and walls of many poliomyelitis units, so that tracheotomies and catheterizations usually invited trouble. I can talk about using Chloromycetin or some other drug prophylactically when the patient under discussion was placed in the respirator or even earlier, but in practice the decision depends on the local situation and is a matter of individual judgment. Obviously, the indications for prophylactic chemotherapy have to be weighed carefully against the dangers of emergence of persistent strains and of altering the patient's flora. I am sure if this patient had received chemotherapy earlier and then had a *P. vulgaris* septicemia, I might wisely say that the physicians produced it because they had eradicated the normal flora and allowed the organism to grow. At least I cannot make that latter remark.

On the twenty-seventh day the hypotension that developed appeared too late to be the result of nervous-system damage and was probably related to the shocklike picture secondary to suffocation.

Jaundice developed two days after Thorazine was given. I have not had much experience with Thorazine jaundice in children and was able to find 1 report of jaundice developing in an adult within twenty-four hours after 50 mg. of intramuscular injection of Thorazine. The fact that the phosphatase was not markedly elevated is against the Thorazine type of plugging of bile canaliculi. The elevated transaminase level does not help me. There was no evidence for cardiac damage, but any muscular disease may produce an elevated transaminase. Therefore, in the presence of the severe muscular involvement that this patient must have had, I do not believe I can consider the transaminase elevation indicative of liver involvement. The cholinesterase was 0.33 pH units. Is this within the range of variation in the laboratory here? That determination has a considerable normal range. Those who work with that determination always stress the fact that a single low value is not reliable, but that repeated determinations are of value for following the course of apparent involvement.

DR. DANIEL S. ELLIS: We should consider this level to be low.

DR. BERENBERG: That would tend to make me believe that this was hepatitis of a hepatocellular type rather than of a Thorazine variety. Did the patient have eosinophilia or a positive flocculation?

DR. ELLIS: She had no eosinophilia.

DR. BERENBERG: That, too, would argue somewhat against Thorazine toxicity.

DR. ELLIS: She had a positive cephalin flocculation.

DR. BERENBERG: That does help. I think I can say that this was not Thorazine toxicity.

The terminal event was probably the result of increasing stenosis, with plugging of the tracheobronchial tree and repeated suffocation. One should consider terminal ulceration of the intestinal tract, which, if it was of a Cushing–Rokitansky type, should have appeared sooner. Those cases described in poliomyelitis by Cook et al.[1] all occurred within the first several days of the illness. Pulmonary embolus from thrombophlebitis has to be considered. I should say that this woman had bulbospinal poliomyelitis and progressive tracheobronchial stenosis due to trauma in some degree and to *Staph. aureus* to a considerable degree. There was no evidence of an anomaly that would have predisposed to stenosis. In addition there was generalized sepsis, involving the trachea, the lungs, the parotid gland, the bladder and the liver, septicemia and thrombophlebitis. Is there any finding in the films that will contribute?

DR. CASTLEMAN: They were normal.

DR. BERENBERG: I assume that the films were taken with the portable machine.

DR. JOSEPH HANELIN: That is correct. A series were taken both before and after tracheotomy. The lungs were clear in these films.

DR. BERENBERG: I would be surprised if the lungs were normal at autopsy.

DR. HANELIN: I do not know when the last film was taken.

DR. BERENBERG: I think that at the time of death the patient had pneumonia and possibly pulmonary spread of the tracheobronchial infection.

DR. HANELIN: The films do not show obvious parenchymal disease.

DR. CASTLEMAN: Dr. Ellis, you followed this patient; have you a comment?

DR. ELLIS: It is helpful to have Dr. Berenberg review this story and give us an objective point of view. Those of us who cared for the patient were confronted with one crisis after another; at times it was difficult to be sure that we were not treating ourselves rather than the patient. She lived as long as she did only by the diligence and devoted attention of the house staff, who were never more than 15 feet from the respirator.

I should like to discuss two points that Dr. Berenberg raised. One is the frequent bronchoscopies. Without any question we tried to withhold bronchoscopy because we were aware of its dangers. The patient frequently requested aspiration of the bronchial tree because of severe suffocation; we soon discovered that she was correct in demanding bronchoscopy because after each one she was better and the tidal air volume increased even when only a small amount of material was aspirated. At the end we were desperate: if we bronchoscoped, we removed very little material; if we did not, she became cyanotic and went into collapse. The first large clot of blood — a 4-cm. plug — was removed three or four days after the tracheotomy. We thought that that blood probably oozed from the tracheotomy itself. Consequently, when granulation and stenosis occurred we were surprised. When we removed the crusts, which had to be removed with the forceps, more bleeding occurred. If we did not remove them, they caused obstruction. We considered infection, Tridione sensitivity, Alevaire sensitivity and irritation from the catheter itself as possible causes of the stenosis. We withdrew all treatment except warm, moist heat and the catheter suction of the tracheotomy tube, which we had to continue. We stopped Chloromycetin at the end of six days because of a generalized rash, which we thought to be a result of drug sensitivity. The response of the temperature and clinical course was better to neomycin than to any other antibiotic given.

It is possible that the Thorazine caused the jaundice. We considered massive pulmonary infarcts, generalized septicemia and hepatotoxic reaction from the septicemia as well. I favored the last possibility as the cause of the jaundice. Dr. Austen gave this patient constant care; he may have an additional comment.

DR. FRANK K. AUSTEN: Jaundice has been reported in patients with poliomyelitis and respiratory paralysis requiring ventilatory assistance.[2] These workers observed a fall in serum albumin, a rise in bromsulfalein retention and urobilinuria in many patients. A few cases showed prolongation of the prothrombin time, and 10 patients had manifest jaundice. Hepatic congestion due to impaired venous return from mechanical ventilation was a suggested cause. Nutritional deficiency or liver damage from the virus (poliomyelitis) itself has not been ruled out.

One other patient from whose trachea *Staph. aureus* was cultured required frequent bronchoscopies and on one occasion was relieved of a plug 4 cm. in diameter. It is not clear why this patient recovered and the patient under discussion did not.

DR. BERENBERG: What method of humidification did you use?

DR. AUSTEN: Simply a humidifier that produced warm, moist air or oxygen.

DR. BERENBERG: Did you have a direct connection?

DR. AUSTEN: Yes; the trachea was humidified through the tracheotomy.

### CLINICAL DIAGNOSES

Paralytic spinal poliomyelitis.
Tracheobronchial obstruction.

### DR. WILLIAM BERENBERG'S DIAGNOSES

Bulbospinal poliomyelitis.
Tracheobronchial stenosis, as result of trauma and *Staph. aureus* infection.
Generalized septicemia.
Thrombophlebitis.

### ANATOMICAL DIAGNOSES

*Acute anterior bulbar spinal poliomyelitis.*
*Acute and chronic tracheitis and bronchitis, severe.*
*Tracheal stenosis, severe.*
Bronchopneumonia.
Operations: tracheotomy and multiple bronchoscopies.

### PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Just above the bifurcation the trachea was markedly stenotic (Fig. 1); it barely admitted a thin probe. The walls were very thick. The bronchi seemed normal, although they may have been slightly narrowed. The marked narrowing of the trachea was quite a distance below the tracheotomy.

DR. ELLIS: But how far below the end of the tracheotomy tube was the narrowed area?

DR. CASTLEMAN: It began immediately below the end of the tube. In the lungs there were numerous areas of atelectasis and pneumonia. Many of the bronchioles contained secretion and exudate, some of which had organized. If one saw these changes in the bronchioles alone one would think of bronchiolitis fi-

brosa obliterans, an entity that involves the entire lung and produces tiny nodules. Instead, this picture was the result of exudate that had been carried into the small bronchi and caused complete plugging. This process in the lungs was widespread.

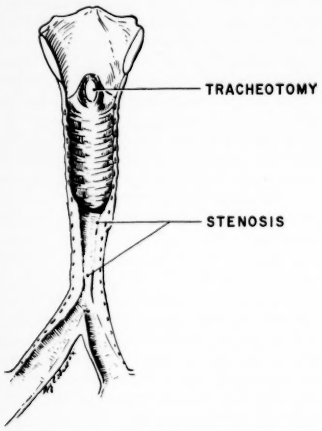


FIGURE 1.

DR. BERENBERG: How old do you think the process was?

DR. CASTLEMAN: It was probably two or three weeks old.

The microscopical sections of the trachea showed thickening of the wall and a great deal of inflammation. The epithelial lining of the trachea, which normally is composed of ciliated columnar epithelium, was made up of stratified squamous-cell epithelium. Apparently, after the ulceration, regeneration with good stratified squamous epithelium occurred. The major bronchi below the trachea had exactly the same appearance; their inner lining was composed of only a small amount of normal epithelium and of squamous cells as the result of regeneration.

There was no evidence of sepsis anywhere else in the body. The liver, the kidneys and all the other viscera were normal. Blood cultures were negative. The infection was limited to the respiratory tract.

DR. ELLIS: Can you make any deductions about the cause of the stenosis?

DR. CASTLEMAN: Probably, it was a result of a combination of infection and the bronchoscopies. Dr. Benedict, do you have any comment about the bronchoscopies?

DR. EDWARD B. BENEDICT: No; but I do not think they would be traumatizing through a tracheotomy stoma; they are easy to do.

DR. ELLIS: Rather than the bronchoscopy, I should think the constant suctioning and the rubber catheters played a part, particularly since the stenosis began below the tracheotomy tube, where the catheter had irritated the wall.

DR. CASTLEMAN: Dr. Richardson, will you describe the spinal cord?

DR. EDWARD P. RICHARDSON, JR.: The central-nervous-system lesions due to poliomyelitis were severe and extensive. At all levels of the spinal cord, nerve cells in the anterior horns of the gray matter and in the adjacent portions of the posterior horns were completely destroyed, and there frequently was necrosis of all tissue elements with cavitation in these regions of the gray matter. These lesions contained innumerable macrophages filled with the breakdown products of the destroyed parenchyma. The walls of the blood vessels were heavily infiltrated with lymphocytes. The changes at the higher levels of the neuraxis were less pronounced. There were mild neuronal lesions, with collections of perivascular lymphocytes in the tegmentum of the brain stem, and, as is typical of poliomyelitis, there was destruction of the large pyramidal motor cells of Betz in the motor cortex. The cerebral cortex was otherwise normal. An unusual feature of this case, undoubtedly the result of its duration and the severity, was severe nerve-fiber degeneration in the lateral and anterior white columns of the spinal cord, which contained fat-filled macrophages, secondary to the loss of the nerve cells. Similar changes in lesser degree were also found in the posterior columns of white matter next to the posterior horns. The neuropathological findings clearly indicate that if the patient could have survived the tracheobronchial and pulmonary complications, she still would never have been able to move any of the skeletal muscles below the neck.

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## PROGRESS IN ANTIBIOTICS DURING 1955

ALTHOUGH 1955 was not marked by any outstanding advances in the development of radically new principles or greatly superior agents in the field of antimicrobial therapy, interest in this area continued to be quite active. This is well documented in the record of the Third Annual Symposium on Antibiotics that was held in Washington, November 2-4, under the joint sponsorship of the Antibiotic Division of the Food and Drug Administration, Department of Health, Education and Welfare, and the journals *Antibiotics and Chemotherapy* and *Antibiotic Medicine*. All the 150 papers presented and the verbatim transcriptions of the three panel discussions held at that symposium are now available in full in the volume, *Antibiotics Annual, 1955-1956,* published under the joint editorship of Dr. Henry Welch, who was chairman of the symposium and arranged its program, and Dr. Felix Martí-Ibáñez.

As in previous years, a large proportion of the papers — actually, a third of them — were contributed from the research laboratories of drug manufacturers; a similar number were by workers in university laboratories or clinics, and most of the rest were reports from independent or Government-supported hospitals and laboratories. This year the symposium also took on an international character, 17 of the papers being presented by foreign workers from both commercial and university laboratories, reflecting to some extent the increased clinical, scientific and economic interest in antibiotics outside this country.

Except for a few papers that concerned the broad relation of antibiotics to nutrition, genetics, viral diseases and infections in general, the material presented was specifically oriented about a few central themes. One of the subjects discussed was the need for, or the usefulness of, combinations of vitamins with broad-spectrum antibiotics, and the question was far from settled. Some 9 papers dealt specifically with this subject; they showed only that such combinations can be administered without apparently increasing the untoward effects of the antibiotics or clearly decreasing their clinical efficacy, but there was no definite demonstration that any additional benefit was derived. The keynote on this aspect was struck by Dr. Grace A. Goldsmith, of Tulane University, in her review, which has already been reprinted in an earlier issue of the *Journal*[1] and commented on editorially in the same issue.

Another group of papers dealt with the resistance of bacteria to antibiotics, including more data on the prevalence and epidemiology of antibiotic-resistant staphylococci and the emergence of resistant strains of other bacteria during prophylactic use of antibiotics. Methods of testing for susceptibility of organisms and technical problems of screening for antibiotic activity were also discussed.

The prophylactic uses of antibiotics were presented in 16 separate papers, and various aspects were also

considered during part of one of the panel discussions. Most of the formal papers on this aspect dealt with the use of antibiotics in preparation for surgery of the bowel; the superiority of neomycin by mouth for this purpose was generally acclaimed, although some of the data were interpreted as favoring the use of this antibiotic in combination with one or another of the tetracyclines. Data were also presented that confirmed the well known efficacy of penicillin in the prophylaxis of streptococcal infections, particularly in interrupting the progress of epidemics of such infections and in preventing recrudescences of rheumatic fever. The use of intramuscular injections of benzathine penicillin G in proper dosage and at appropriate intervals was confirmed as being as effective as daily oral doses of soluble salts of penicillin G.

Long-term administration of antibiotics for chronic infections of the respiratory or urinary tract was also considered in the panel discussion. In cases of cystic fibrosis of the pancreas ("pulmonary viscidosis"), more or less continuous administration of sulfadiazine or one of the tetracyclines or, when these proved ineffective, a combination of chloramphenicol and erythromycin was recommended to begin as soon as the condition is recognized and to be interrupted only after long periods of good health and freedom from infection. In other chronic respiratory infections and in chronic urinary-tract infections, although some degree of suppression has frequently been achieved with continuous administration of antibiotics, it was conceded that the fundamental problem — that of coping with the underlying and predisposing causes of these infections — deserved primary attention.

A large number of the papers dealt with additional data on the use of antibiotics that have already become established, such as erythromycin, the tetracyclines, neomycin and the more recently introduced cycloserine. Some 8 papers and part of one of the panel discussions concerned the administration of the last-named agent in tuberculosis and in other infections, particularly those of the urinary tract. Although in most of these reports the results were interpreted as being favorable, it was not clearly shown that this agent was sufficiently useful to warrant the considerable risk of serious toxic effects on the central nervous system that its administration entailed, except in serious infections in which other antibiotics had failed.

The toxicity of various antibiotics was also specifically considered in several papers and in one of the panel discussions. Evidence was presented from experiments in animals that suggested that the bone-marrow depression from chloramphenicol was related to diminished intake of food or to malnutrition. Anaphylactic deaths from penicillin were shown to be rare, considering the tremendous numbers of persons being treated and the enormous amounts that are used; these fatal cases have occurred predominantly from injection of repository preparations, and only 1 case was known in which death resulted from an oral dose. The members of the panel all agreed that the true incidence and significance of undesirable reactions from antibiotics is not known, and furthermore, is very difficult to ascertain.

Several new antibiotics were revealed, and data concerning them and about new uses of others that had recently been introduced were presented, but the importance of most of them could not be assessed because of the absence or paucity of clinical data. Some of the new antibiotics had activity similar to that of erythromycin and exhibited crossresistance with that agent. There were also several new antifungal agents, most of them being too toxic for clinical use. Evidence was presented that puromycin, an agent previously shown to have some oncostatic activity, may be effective in certain parasitic infestations.

A large number of papers, 14 in all, concerned nystatin, an antifungal agent introduced some time earlier (about which a number of papers had already been published) and already being exploited commercially. Chief interest in this agent centered about its use in combination with broad-spectrum antibiotics — tetracycline in particular — to prevent the occurrence of monilial infections as a complication of treatment. An advertising campaign by the manufacturers to encourage such use was already well advanced.

In the papers presented, it was clearly shown that nystatin could indeed reduce the numbers of *Candida albicans* and of some other fungi and yeasts in the feces after oral administration of that agent, with or without tetracycline. The evidence also supported the usefulness of nystatin in the treatment of moniliasis, particularly when the antibiotic was applied topically or when given orally for infections of the alimentary canal and perhaps also in systemic moniliasis. When used in combination with tetracycline, moreover, it did not seem to increase the number of untoward reactions. However, the evidence that this combination had any effect beyond reducing the numbers of fungi and yeasts that could be cultured during treatment was scanty and not too convincing from the controlled studies that were presented.

In an editorial review of these papers, Welch[2] concluded that since serious monilial infections are likely to develop in some specified groups of patients, particularly those with chronic debilitating or terminal illnesses that require long-term treatment with broad-spectrum antibiotics, the use of nystatin was proper and should be helpful in such cases, but it should not be given to all patients receiving broad-spectrum antibiotics. This, however, requires clinical judgment and can be considered a justifiable and specific use of nystatin but not a justification or indication for a fixed combination of that antibiotic with any others.

Among the new antibiotics that were unveiled at this symposium were two that were discovered independently in the research laboratories of different manufacturers, and each of which was derived from a hitherto undescribed species of streptomyces. Both

were highly active against strains of staphylococci and several other bacterial species and showed no crossresistance with other available antibiotics. Studies in another laboratory indicated that these two antibiotics had identical activities and showed complete crossresistance, suggesting that they were probably the same agent or closely related ones. Subsequently, these two antibiotics, one of them introduced under the generic name of streptonivicin and given the trade name of Albamycin and the other introduced under the name of Cathomycin and now carrying this as its trade name, have since been shown to be the same,[3] and both have been given the generic name of novobiocin.

The only other recently introduced antibiotic that received a good deal of attention was penicillin V. The superiority of this new type over penicillin G in any form for oral therapy was generally confirmed and shown to be related to its better absorption. However, owing to greater enzymatic inactivation of penicillin V as compared with that of penicillin G in the tissues, there was some question whether the duration of action of the former was greater than that of the latter. This greater inactivation in the tissues accounts for the inferiority of penicillin V for parenteral use.

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3. Welch, H., and Wright, W. W. Common identity of cathomycin and streptonivicin. *Antibiotics & Chemother.* **5**:670-673, 1955.

## THE CHANNING HOME

THE Channing Home over the past ninety-eight years has become a tradition in the Greater Boston area as a refuge for chronically ill female patients. Founded in 1857 by Harriet Ryan Albee, who had previously been performing this act of charity in her home at her own expense, this institution has enlarged several times to increase the scope of its service. Even in Harriet Albee's era, however, advanced and usually terminal cases of tuberculosis predominated among the patients.

The first quarters of the Home, in the vacant vestry of Dr. William Ellery Channing's church, were provided by its charitable rector, Dr. Ezra Garnett. Dr. John H. Borland, assisted by Dr. Samuel A. Green, and Dr. Charles W. Homans, were its first physicians. Through the years, famous names in Boston medical circles have been associated with this institution—Ayer, Blake, Bowditch, Cabot, Cheever, Cutler, Greene, Lord, Morrison, Munroe, Pratt, Richardson, Sears and Smith, to mention but a few.[1] In 1859, the South Street "Channing Home" was incorporated. Two years later more patients found accommodations on McLean Street. Here, in 1873, Mrs. Albee herself suffered and died of the disease whose pangs she had striven to soften for others, her pioneering efforts being memorialized by James De Normandie, D.D., minister of the First Church in Roxbury.[2]

Since 1907, when the Channing Home opened its doors on Pilgrim Road in the Fenway, its facilities have been devoted exclusively to the treatment of tuberculosis, and finally in January, 1956, its program was expanded to include male patients. This extension of service to the community was undertaken by the trustees on advice from its staff that such private facilities were needed in this area. The nearest care of this type was in New Bedford, and distance divided families at a time when great adjustments in their lives should be keeping them close. The policy of caring for all according to their means is continued.

An active staff aided by a consulting staff offers the latest therapeutic advances in the treatment of tuberculosis. Necessary thoracic surgery is performed in neighboring hospitals and convalescence is continued at the Channing Home. Biweekly staff meetings re-evaluate each case to individualize the treatment to the patient and to the disease. A member of the staff supervises daily progress and helps to solve its problems, backed by an excellent group of nurses and with radiologic and laboratory assistance. Channing can rightfully claim to be a friendly, educational organization, where patients learn to accept and live with their disease — still an important factor in the treatment of tuberculosis.

A wealth of well documented clinical material has accumulated over the years, started by the careful clinical observations of Dr. Borland. This is being used to teach undergraduate and postgraduate medical students as well as for research. Articles by members of the staff have appeared in this journal[3] and the *American Review of Tuberculosis*[4] evaluating the Home's experience. The recent grant by the Ford Foundation gives recognition to the caliber of its work.

By offering the institution's advantages to male patients as its centennial approaches, the trustees, staff, nurses and all its personnel expect to expand further the community service that it has offered over the years so that the next hundred years will be as rewarding as the past. Certainly, a more optimistic future for the patient can be predicted than that described by Nathaniel Frothingham, Ralph Waldo Emerson and Oliver Wendell Holmes, as well as by James Russell Lowell[5] in his reference to the Channing Home of 1859:

> Of souls that shivered on the edge
> Of that chill ford repassed no more,
> And in their mercy felt the pledge
> And sweetness of the farther shore.

### References

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## BOSTON UNIVERSITY SCHOOL OF NURSING

BOSTON University, in its continuing effort at increased service to the community, has created the post of Director of University and Community Relations for the School of Nursing, and has been fortunate in securing Dr. Esther Lucile Brown as first incumbent of the office. This action is in line with the general trend toward elevating the academic standing of nursing education, in which Yale University has taken such a prominent part.[1]

In her new role Dr. Brown, according to a joint statement by President Harold C. Case of Boston University and Dr. Donald Young, president of Russell Sage Foundation, will cultivate closer relations between the School of Nursing and the various professional schools and agencies in the medical and health fields, with improved patient care as the final objective.

Dr. Brown is best remembered as director of the field studies undertaken by the Russell Sage Foundation for the National Nursing Council, the results of which are embodied in her book *Nursing for the Future*,[2] published in 1948, when the Boston University School of Nursing was but two years old. A graduate of the University of New Hampshire, Dr. Brown received the degree of Doctor of Philosophy in cultural anthropology and sociology at Yale University. By training and experience she is eminently qualified for her new and important position.

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## DISASTER PLANNING

UNLESS there should be an all-out and thorough enemy attack, it is unlikely that the majority of this country's hospitals will ever be faced with the necessity of effecting the abrupt transition from a disaster plan on paper to one of actual performance.

That the transition had to be made in recent months by hospitals in Worcester, Lynn, Salem and Waterbury, Connecticut (in an area considered at one time at least reasonably free of weather-inspired disasters) is evidence enough, however, to support the recommendations of the American Hospital Association that every hospital in the nation prepare adequately for *local* disasters, thus reducing the problem of preparing for disasters of *national* scope.

Dr. Dean A. Clark, consultant to the Committee on Disaster Planning of the American Hospital Association, stated at the New England Hospital Assembly held in Boston in March that a prearranged adequate and functional disaster program may well be one of the requirements for accreditation by the Joint Commission on the Accreditation of Hospitals.

To highlight its current campaign for the establishment of disaster plans in the nation's hospitals, the American Hospital Association has designated disaster planning as the theme for National Hospital Week, May 6–12.

What the Association will promote through the common medium of designating special weeks for special purposes is summed up neatly by Dr. Clark as follows:

> Disaster planning is not the product of the imagination of a science fiction writer, but rather the basic realization of a possibility which exists in the country as a whole and in every city and community. The hospitals themselves are ultimately responsible, but can only have a workable and successful program with the cooperation of the local businessmen and citizens.

*A lady in Tennessee had a gold filling, about the size of a squirrel shot, recently removed from the side of her neck, immediately below the angle of the jaw . . .* — American Journal of Dental Science.

Boston M. & S. J., *May 1, 1856*

## MASSACHUSETTS MEDICAL SOCIETY

### DEATH

QUINN — James H. Quinn, M.D., of Springfield, died on March 6. He was in his seventy-fifth year.

Dr. Quinn received his degree from Georgetown University School of Medicine in 1907. He was a member of the board of trustees of the Springfield Municipal Hospital and a fellow of the American Medical Association and the American College of Physicians.

He is survived by three brothers and four sisters.

## MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

### CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

| ORTHOPEDIC CLINIC | DATE | CLINIC CONSULTANT |
|---|---|---|
| Haverhill | May 2 | William T. Green, M.D.; and Henry Banks, M.D. |
| Greenfield | May 3 | Charles L. Sturdevant, M.D. |
| Lowell | May 4 | Albert H. Brewster, M.D. |
| Salem | May 7 | Paul W. Hugenberger, M.D. |
| Brockton | May 10 | George W. Van Gorder, M.D. |
| Gardner | May 14 | Carter R. Rowe, M.D. |
| Lynn* | May 14 | Daniel M. Killoran, M.D.; and John J. Crowley, M.D. |

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Clinic.

| | | |
|---|---|---|
| Pittsfield | May 16 | Edward J. Coughlin, Jr., M.D. |
| Springfield | May 17 | James D. Fisher, M.D. |
| Worcester | May 18 | John W. O'Meara, M.D. |
| Hyannis | May 24 | Paul L. Norton, M.D. |
| Fall River | May 28 | David S. Grice, M.D.; and Arthur W. Trott, M.D. |

| RHEUMATIC-FEVER CLINIC | DATES |
|---|---|
| North Reading | May 1, 8, 15, 22, 29 |
| Fitchburg | May 2, 9, 16, 23 |

| PLASTIC CLINIC | HELD | CONSULTANT |
|---|---|---|
| Eastern Massachusetts | Semi-monthly | Bradford Cannon, M.D.; and Joseph E. Murray, M.D. |
| Western Massachusetts | Monthly | Joseph M. Baker, M.D. |

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

## CORRESPONDENCE

### REGARDING GIVING

*To the Editor:* The *Journal* has devoted space so generously to communications from the National Foundation for Infantile Paralysis and to the subject of poliomyelitis, for which we are indeed grateful, that I hesitate to address an additional comment on the interesting editorial, "Dividing the Charity Dollar," which appeared in the January 19 issue of the *Journal*.

However, as the editorial itself states concerning a previous editorial ("E Pluribus Unum"), which was "widely quoted and widely misinterpreted," it is more than possible that the present editorial will have a similar fate. Editorial comment in the *New England Journal of Medicine* appears to carry great influence.

The scale of "relative importance" of specific pathologic conditions and disorders, on whatever basis such a scale is constructed, is apt to be a misleading gauge for contributions to or *participation* in the activities of a voluntary health organization. The construction of any such scale is fraught with technical difficulties, even without consideration of the frame of reference on which it is built. Is incidence, prevalence, mortality, curability, preventability, disability or any one of a score of other factors to be taken as the dominant consideration in the scale?

Indeed, the use of any such scale is to misread the function and the history of that peculiarly American institution, the voluntary health agency.

To the best of my understanding a voluntary health agency is *not* a charitable institution, except by legal definition, in the old-fashioned sense of "giving to the poor." There is a semantic problem here, but the structure of American society has changed to the extent that the "Lady Bountiful" concept of charity is no longer tenable. To the extent that the word charity still means "love of one's fellow man," voluntary health organizations may be considered charitable institutions. But this is their goal and not their *modus operandi*.

Voluntary agencies are really self-help organizations in the framework of a democratic society. They are organized partnerships between the professions, primarily the medical profession, and the public to achieve a goal by which the professions and the public will both benefit.

The judgment to be pronounced upon any voluntary health agency, and co-ordinately the amount of public and professional support and participation it obtains, should not be based on its distance from its goal.

Many specific criteria can be laid down for evaluating a voluntary health agency, but they should certainly include the following:

How well organized is the agency? (Or what is its leadership?)

How effectively does it spend its money? (*Not*, How does it raise funds?)

What is its history? (Or why does the public join hands with the profession in hope for an early and satisfactory solution to its self-appointed challenges?)

It must be recognized that voluntary associations for assault on problems of disease are social instruments of a new kind and must be employed intelligently.

No disease as a disease has "emotional appeal"; to many people all disease is repulsive. The appeal of a voluntary health organization lies in the hope and the prospect that something wise can be done to meet the challenge of the disease. The public responds to the possibility that it can help "do something."

There is a false impression that the picture of a crippled child is "appealing." The picture has "appeal" only when it shows that the child is being or has been helped — for example, wearing braces or being carried. In this connection one may recall perhaps the most appealing of all campaign posters, the picture of a tired little boy being carried by a tattered and slightly larger boy. The caption reads: "He ain't heavy; he's my brudder."

Public participation in and gifts to a voluntary health organization often relieve an unspoken frustration of standing helpless in the presence of disease. The physician is not subject to the same degree of frustration because he is in the unique position of being able to do something, or at least to determine whether anything should be done, for the patient facing him. The "appeal" of a specific voluntary health organization lies in public acceptance of the fact and extent to which it is really "doing something" — something intelligent — about the problem that it has been organized to face.

Public support of a voluntary health agency is based on its confidence that the organization will expend its contributions of time and money wisely and well. Such confidence can be based only on the history of the organization, not the history or magnitude of the disease. The March of Dimes, which is the fund-raising arm of the National Foundation for Infantile Paralysis, enjoys this confidence. It is based upon public reaction to specific programs of research, education and service (financial aid) to victims of paralytic poliomyelitis. Much of the so-called "success" of the March of Dimes is based upon its frank disclosures to the public (long before there was a vaccine) of the program that it was supporting.

The public supports what it understands — both through voluntary contributions and through tax funds. The National Institutes of Health budgets for research have little difficulty in passing Congress: "research" is a good word. The limitation here (in research) is brain power, not money. It is also true that Congress appropriates money more readily for the control of diseases in which there is a widespread and organized public interest.

Hence, the voluntary health agency is an educational organization of the first importance. By its very nature, much of its most effective educational work is intimately associated with its fund-raising activities. The "gift" is a token that the giver is satisfied that he knows what the organization is doing. There is much "unmotivated giving" — prompted by the belief that the particular cause is a "good thing." But such giving takes the heart out of the basic educational function of the voluntary health agency.

There is a view abroad that multiple campaigns for disease-control agencies are a "nuisance." This point of view has validity only if one accepts the premise that being educated is a nuisance and that it is better to be ignorant.

The weakness in the social effectiveness of joint or federated fund-raising campaigns is that they must depend upon unmotivated giving; they give little information or opportunity for participation in activities in return for the money given. They water down information to its lowest level. When their campaign "points" are specific, they must be capriciously selective. Then they are no longer joint campaigns with any educational significance but rather specific campaigns in which a load of cars is hitched to the locomotive appeal of one or two specific goals.

The competition among voluntary health agencies for support is a healthy thread in the social fabric. It is healthy because it is educational, voluntary and frankly public. There is no secret diplomacy or juggling of budgets and

vanities behind closed doors. Furthermore, the public is free to withdraw or refuse its support the moment it loses confidence in an organization and its program.

It is on the basis of such considerations that the National Foundation for Infantile Paralysis has adopted a policy of not entering into federated fund-raising drives.

HART E. VAN RIPER, M.D.
*Medical Director*
National Foundation for Infantile Paralysis, Incorporated
New York City

*Note:* Those who favor co-ordinated rather than competitive campaigns do not think of the multiple independent ones so much as nuisances as threats to the equitable distribution of the available funds. True, more intensive campaigns can bring forth greater returns, but the distribution will remain unequal and the solicitation is competitive.

It is possible that the existing agencies, by pooling their genius for publicity and their great resources for fund-raising, can even increase the total harvest and help to direct it into the various channels where it would be of greatest value. Joint plans may not at present be effective, but they might be made so if compassion were put on a community basis.

As Dr. Van Riper says, the public supports what it understands. This could be qualified by the statement that the public supports what it believes it understands, and the educational campaign should be a really comprehensive one. —ED.

## REGARDING CLINICOPATHOLOGICAL EXERCISES

Something that has occurred to me time and again during my attendance and occasional participation in clinicopathological conferences is that we do not go far enough and that we do not learn all that we might from them. It seems that if we asked and tried to answer a few questions after the pathologist had given the diagnosis, something valuable would be added. These are the questions:

If the diagnosis had been made ante mortem (of course, autopsy showed that it had not been made then) would treatment have made a difference in the outcome? Could treatment based on correct diagnosis have prolonged life?

If an identical case were seen the next day, how would it be managed?

What laboratory procedures proved of value in correct diagnosis, and which ones could have been omitted?

These suggestions may appeal to some physicians as having merit. For all I know, such questions may be asked routinely in some hospitals, but in the few community and few university hospitals with which I am familiar, the discussion usually ends with the pathological diagnosis.

I am aware that the purpose of conferences on therapy is to take care of that aspect of study. But it does seem that what I propose would make for a really complete examination of every aspect of the disease under consideration at these conferences, and the cumulative experience, as reviewed at the end of stated periods, might lead to the minimum effective treatment of each disease discussed. The practical and immediate value of relating therapy to the completed case at hand seems apparent, and ought to benefit future patients.

I am sure that the constructive criticism implied in this communication is clear. A running commentary on what is being accomplished will make for better physicians, and at the same time point the way, day by day, how to continue and where to change course.

VICTOR KNAPP, M.D.
Asbury Park, New Jersey

## DOCTOR'S FINAL CONTRIBUTION

*To the Editor:* To a medical student, the cadaver he dissects represents the opening chapter in the book of his professional life. But some medical colleges are short of cadavers for students. Why should not each one of us contribute one cadaver, our own body, as soon as we are through with it?

Our civilization is in the habit of destroying an important educational asset and then lamenting its scarcity and expense!

What prevents us from directing that upon death, our remains be well embalmed and given to a medical college instead of being buried or cremated?

For each doctor to prearrange that *post obitum* his body is to be given to the medical school of his choice appears to be so simple and so natural as to have been altogether overlooked.

The legal procedure necessary for directing that one's remains shall become the property of a medical college is, first of all, that one must make one's own personal request. No relative can make this disposition, legally, in the Commonwealth of Massachusetts. Since state laws differ, wherever there is a shortage of material for medical education, as in Massachusetts, persons in remote areas will need to acquaint themselves with the laws of their own states. In Massachusetts, a form such as the following would be legal:

I HEREBY REQUEST THAT AS SOON AS PRACTICABLE AFTER MY DECEASE AND FUNERAL, MY BODY SHALL BE GIVEN TO THE DEAN OF SCHOOL OF MEDICINE.*

Signed .....
Witnessed by .....
Date .....

*Name the school of your choice.

Secondly, one should arrange for the legal form of request to be placed in the hands of one's funeral director and for him to call the office of the dean of the medical school and obtain acceptance of the body and directions for its delivery which he shall follow out.

SARAH PARKER WHITE, M.D.
Boston

## SUSPENSION OF LICENSE

*To the Editor:* At a meeting of the Board of Registration in Medicine held March 1, 1956, it was voted to suspend the registration of Dr. Louis E. Schraffa, 10 Bennington Street, Boston, for five months beginning April 1, 1956.

ROBERT C. COCHRANE, M.D., *Secretary*
Board of Registration in Medicine
State House
Boston

## RESTORATION OF LICENSE

*To the Editor:* At a meeting of the Board of Registration in Medicine held March 11, 1956, it was voted to restore the registration of Dr. Earl G. Hersey, Milton, Massachusetts.

ROBERT C. COCHRANE, M.D., *Secretary*
Board of Registration in Medicine
State House
Boston

# BOOK REVIEW

*Subacute Bacterial Endocarditis.* By Andrew Kerr, Jr., M.D. 8°, cloth, 343 pp., with 7 illustrations, 2 charts and 1 table. Springfield, Illinois: Charles C Thomas, 1955. $6.50. (Publication No. 274, *American Lecture Series.*)

Every few years, a monograph on subacute bacterial endocarditis appears and brings the subject up to date. This book, which is a thorough report on the subject, should be read by all students of the disease. There is an excellent historical account of bacterial endocarditis and a fine description of the clinical picture, the course of the disease

and the results of modern therapy. The bibliography is extensive, and the index adequate.

As one who has witnessed the unfolding of knowledge about bacterial endocarditis during the past thirty-five years and has seen such a remarkable change in the outlook for a patient with this infection, I can say that great advances have been made and that the results are almost unbelievable.

Dr. Kerr has made a real contribution to the literature on this important subject.

CHESTER S. KEEFER, M.D.

## BOOKS RECEIVED

**The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.**

*Chlorpromazine and Mental Health: Proceedings of the symposium held under the auspices of Smith, Kline and French Laboratories, June 6, 1955, Warwick Hotel, Philadelphia.* 8°, 200 pp., with 14 illustrations and 25 tables. Philadelphia: Lea and Febiger, 1955. $3.00.

*Surgery of the Sympathetic.* By Alexander Lee McGregor, F.R.C.S. (Eng.), M.Ch. (Edin.), consulting surgeon, Johannesburg General Hospital, and honorary research associate, Department of Surgery, University of the Witwatersrand. 8°, cloth, 192 pp., with 101 illustrations and 6 tables. Bristol: John Wright and Sons, Limited, 1955. $7.00. (Distributed by Williams and Wilkins, Baltimore.)

*Ratschläge für den Prostatiker und seinen Arzt.* By Prof. Dr. Eduard Pflaumer. 8°, paper, 31 pp., with 13 illustrations. Stuttgart: Georg Thieme, 1955. DM 3.75.-$0.90. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

*Modern Nutrition in Health and Disease: Dietotherapy.* Edited by Michael G. Wohl, M.D., chief of human nutrition, Division of Biological Chemistry, Hahnemann Medical College and Hospital, and chief of Nutrition Clinic, Philadelphia General Hospital; and Robert S. Goodhart, M.D., scientific director, National Vitamin Foundation, Incorporated, physician-in-charge, Washington Heights Nutrition Clinic, New York City Department of Health, and lecturer in nutrition, School of Public Health, Columbia University. 8°, cloth, 1062 pp., with 80 illustrations and 127 tables. Philadelphia: Lea and Febiger, 1955. $18.50.

*The Lacrimal System: Clinical application.* By Everett R. Veirs, M.D., chief, Section of Ophthalmology, Scott and White Clinic, Scott and White Memorial Hospitals, and Scott, Sherwood and Brindley Foundation, Temple, Texas, professor of ophthalmology, University of Texas Postgraduate School of Medicine, Temple Division, and chief oculist, Gulf, Colorado and Santa Fe Hospital, Temple, Texas. 4°, cloth, 159 pp., with 73 illustrations. New York: Grune and Stratton, 1955. $7.50.

*Hypnotic Suggestion: Its role in psychoneurotic and psychosomatic disorders: A thesis.* By S. P. Van Pelt, M.B., B.S., president, British Society of Medical Hypnotists, and editor, *British Journal of Medical Hypnotism.* 12°, cloth, 95 pp., with 3 illustrations. New York: Philosophical Library, 1956. $2.75.

*Medical Support of the Army Air Forces in World War II.* By Mae Mills Link and Hubert A. Coleman. 4°, cloth, 1027 pp., with 97 tables, 18 charts, plates and a frontispiece. Washington, D.C.: Office of the Surgeon General, United States Air Force, 1955. $7.00.

*Textbook of the Principles and Practice of Nursing.* By Bertha Harmer, R.N., A.M. Revised by Virginia Henderson, R.N., A.M., research associate, Yale University School of Nursing. Fifth edition. 8°, cloth, 1250 pp., with 269 illustrations, 18 tables and 4 plates. New York: The Macmillan Company, 1955. $7.00.

*Topley and Wilson's Principles of Bacteriology and Immunity: In two volumes.* Vol. I and Vol. II. By G. S. Wilson, M.D., F.R.C.P., D.P.H., director, Public Health Laboratory Service, England and Wales; and A. A. Miles, C.B.E., M.A., M.D., F.R.C.P., professor of experimental pathology, University of London, and director, Lister Institute of Preventive Medicine, London. Fourth edition. 8°, cloth, 2331 pp., with 296 illustrations and 196 tables. Baltimore: The Williams and Wilkins Company, 1955. $24.50.

*Of Research People.* By George E. Burch, M.D., Henderson Professor of Medicine, Tulane University of Louisiana School of Medicine. 8°, paper, 56 pp., with illustrations. New York: Grune and Stratton, 1955. $3.00.

*White Coolies.* By Betty Jeffrey. 8°, cloth, 204 pp., with illustrations by J. P. L. Kickhefer. New York: Philosophical Library, Incorporated, 1955. $3.75.

*Textbook of Pharmacognosy.* By T. E. Wallis, D.Sc. (Lond.), F.R.I.C., F.P.S., M.I.Biol., F.L.S., emeritus curator, Pharmaceutical Society of Great Britain, sometime reader in pharmacognosy, University of London, and Hanbury Gold Medallist, 1939. Third edition. 8°, cloth, 578 pp., with 239 illustrations. London: J. and A. Churchill, Limited, 1955. $8.00. (Distributed by Little, Brown and Company, Boston.)

*Clinical Neurosurgery: Proceedings of the Congress of Neurological Surgeons, New York City, 1954.* Vol. 2. 8°, cloth, 173 pp., with 54 illustrations, 16 tables and a frontispiece. Baltimore: The Williams and Wilkins Company, 1955. $6.75.

*Cybernetics: Circular, casual and feedback mechanisms in biological and social systems: Transactions of the Tenth Conference, April 22, 23, and 24, 1953, Princeton, New Jersey.* Edited by Heinz Von Foerster, Department of Electrical Engineering, University of Illinois, Champaign. Assistant editors: Margaret Mead, American Museum of Natural History, New York City; and Hans Lukas Teuber, Department of Psychiatry and Neurology, New York University College of Medicine. 8°, cloth, 100 pp., with a frontispiece. New York: Josiah Macy, Jr., Foundation, 1955. $2.75.

*Physiology and Pathology of Infant Nutrition.* By L. F. Meyer, M.D., professor of pediatrics, Children's Department, Municipal Hospital "Hadassah," Tel Aviv, Israel; and Erich Nassau, M.D., chief, Children's Department, Central Hospital of the Workers Sick Fund, Afulah, Israel. Translated by Kurt Glaser, M.D., M.S., F.A.A.P.; and Susanne Glaser, B.A. Second edition, completely revised. 8°, cloth, 533 pp., with 61 illustrations. Springfield, Illinois: Charles C Thomas, 1955. $11.50.

*Growth at Adolescence.* By J. M. Tanner, M.D. (Penna.), Ph.D., D.P.M. (London), senior lecturer, physiology, St. Thomas's Hospital Medical School, University of London. 8°, cloth, 212 pp., with 57 illustrations, 12 tables and 11 plates. Springfield, Illinois: Charles C Thomas, 1955. $6.50.

*Life Stress and Essential Hypertension: A study of circulatory adjustments in man.* By Stewart Wolf, M.D., professor of medicine and head, Department of Medicine, University of Oklahoma School of Medicine, and supervisor of clinical activities, Oklahoma Medical Research Foundation; Philippe V. Cardon, Jr., M.D., senior assistant surgeon (R), National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland, and instructor in medicine, Georgetown University School of Medicine; Edward M. Shepard, M.D., instructor in medicine, Cornell University Medical College, and attending physician, New York Hospital; and Harold G. Wolff, M.D., professor of medicine (neurology), Cornell University Medical College, and attending physician, New York Hospital. 8°, cloth, 253 pp., with 38 illustrations and 8 tables. Baltimore: The Williams and Wilkins Company, 1955. $7.50.

*Principles of Psychoanalysis: Their application to the neuroses.* By Herman Nunberg, M.D. With a foreword by Sigmund Freud. Translated by Madlyn Kahr and Sidney Kahr, M.D. 8°, cloth, 382 pp. New York: International Universities Press, 1955. $7.50.

*Protein Malnutrition: Proceedings of a conference in Jamaica (1953).* Sponsored jointly by the Food and Agriculture Organization of the United Nations (F.A.O.), World Health Organization (W.H.O.), and Josiah Macy, Jr., Foundation, New York City. Edited by J. C. Waterlow. 8°, cloth, 277 pp., with 21 illustrations, 19 tables and 23 plates. Cambridge, England: University Press, 1955. $3.50. (Distributed by the Columbia University Press, New York City.)

*Therapy of Fungus Diseases: An international symposium, presented June 23, 24, 25, 1955, by the Division of Dermatology, Department of Medicine, School of Medicine and Medical Extension, University Extension, University of California, Los Angeles.* Edited by Thomas H. Sternberg, M.D., professor of medicine (dermatology) and assistant dean for postgraduate medical education, School of Medicine, University of California at Los Angeles; and Victor D. Newcomer, M.D., associate professor of medicine (dermatology), School of Medicine, University of California at Los Angeles. 8°, cloth, 337 pp., with illustrations and tables. Boston: Little, Brown and Company, 1955. $7.50.

*Hypothermic Anesthesia.* By Robert W. Virtue, M.D., Ph.D., associate professor and head, Division of Anesthesiology, University of Colorado School of Medicine, Denver. 8°, paper, 62 pp., with 2 illustrations and 2 tables. Springfield, Illinois: Charles C Thomas, 1955. $2.50. (Publication No. 275, *American Lecture Series.)*

*The Treatment of Renal Failure: Therapeutic principles in the management of acute and chronic uremia.* By John P. Merrill, M.D., associate in medicine, Harvard Medical School and Peter Bent Brigham Hospital, and established investigator, American Heart Association. 8°, cloth, 238 pp., with 31 illustrations and 16 tables. New York: Grune and Stratton, 1955. $6.75.

*The Relief of Symptoms.* By Walter Modell, M.D., associate professor of clinical pharmacology, Cornell University Medical College. 8°, cloth, 450 pp., with 5 illustrations and 13 tables. Philadelphia: W. B. Saunders Company, 1955. $8.00.

*Peripheral Vascular Disease.* By A. J. Barnett, M.D., M.R.C.P. (Lond.), M.R.A.C.P., assistant director, Alfred Hospital Clinical Research Unit, Melbourne, Australia; and J. R. E. Fraser, M.D., M.R.A.C.P., sometime registrar, Alfred Hospital Clinical Research Unit, Melbourne, Australia. 8°, cloth, 219 pp., with 31 illustrations, 6 tables and 39 plates. Melbourne University Press; New York: Cambridge University Press, 1955. $9.50.

*Praktische Mikroskopie.* By Ewald Schild, founder and leader of the Mikrobiologischen Station of Landeshauptstadt Linz. Third edition. 8°, cloth, 262 pp., with 70 illustrations and 19 plates. Vienna: Wilhelm Maudrich, 1955. $6.00. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

*Biochemistry and the Central Nervous System.* By Henry McIlwain, Ph.D., D.Sc., professor of biochemistry in the University of London at the Institute of Psychiatry (British Postgraduate Medical Federation). 8°, cloth, 272 pp., with 43 illustrations and 33 tables. Boston: Little, Brown and Company, 1955. $9.50.

*Ciba Foundation Symposium on Experimental Tuberculosis: Bacillus and host: With an addendum on leprosy.* Edited by G. E. W. Wolstenholme, O.B.E., M.A., M.B., B.Ch.; and Margaret P. Cameron, M.A., A.B.L.S.; assisted by Cecilia M. O'Connor, B.Sc. 8°, cloth, 396 pp., with 69 illustrations and tables. Boston: Little, Brown and Company, 1955. $9.00.

*Complications of Regional Anesthesia: Etiology, signs and symptoms, treatment.* By Daniel C. Moore, M.D., director, Department of Anesthesiology, Mason Clinic, and chief of anesthesia, Virginia Mason Hospital, Seattle. 4°, cloth, 291 pp., with 51 illustrations and 25 tables. Springfield, Illinois: Charles C Thomas, 1955. $10.50.

*Dermatologie der Mundhöhle und der Mundumgebung: Systematik, Morphologie und Grundzüge der Behandlung.* By Dr. Med. et Dr. Phil. Aloys Greither, lecturer in dermatology, Universität Heidelberg, and physician-in-chief, Heidelberg Universitäts-Hautklinik. With a foreword by Prof. Dr. W. Schönfeld, Heidelberg. 8°, cloth, 262 pp., with 191 illustrations. Stuttgart: Georg Thieme, 1955. DM 39.60-$9.45. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

*Aus-und Weiterbildung in der medizinischen Strahlenkunde. Von Reden und Denkschriften.* Edited by Deutschen Röntgengesellschaft, Society of Medical Radiology and Radiology Research, Incorporated. 4°, paper, 44 pp. Stuttgart: Georg Thieme, 1955. DM 3.60-$0.85. (Distributed in the United States by Intercontinental Medical Book Corporation, New York City.)

*Rheumatoid Arthritis and Psoriasis Vulgaris: Internal and cutaneous manifestations of the permanent endoparasitism in the homo sapiens. Their common etiology, pathogenesis, and specific vaccine therapy.* By Tibor Benedek, M.D., assistant clinical professor of dermatology and syphilology, Stritch School of Medicine, Loyola University, attending dermatologist, Catherine Booth Hospital and Clinics, Salvation Army Medical Center, Chicago, and St. Catherine's Hospital, East Chicago, Indiana, and editor, *Mycopathologia* and *Mycologia Applicata.* 4°, cloth, 308 pp., with 57 illustrations, 22 tables, charts and plates. Chicago: Tibor Benedek, 1955. $12.00. (Distributed by Chicago Medical Book Company, Chicago.)

*On the Nature of Man: An essay in primitive philosophy.* By Dagobert D. Runes. 8°, cloth, 105 pp. New York: Philosophical Library, 1956. $3.00.

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*Handbook of Vital Statistics Methods.* Department of Economic and Social Affairs, Statistical Office of the United Nations. 4°, paper, 258 pp., with tables. New York: United Nations, 1955. $2.50. (*Studies in Methods,* Series F, No. 7.) (Distributed by Columbia University Press, New York City.)

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*Atlas of Bronchial Lesions in Pulmonary Tuberculosis: A clinical and morbid-anatomical study.* By C. Dijkstra, M.D., medical superintendent, "De Klokkenberg" Sanatorium, Breda, Netherlands. 4°, cloth, 128 pp., with 131 illustrations. Springfield, Illinois: Charles C Thomas, 1955. $11.00.

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*Asclepiades: His life and writings: A translation of Cocchi's Life of Asclepiades and Gumpert's Fragments of Asclepiades.* By Robert Montraville Green, M.D. 8°, cloth, 167 pp. New Haven: Elizabeth Licht, 1955. $6.00.

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## NONCLINICAL NOTES

### DR. SPECTOR HONORED

Dr. Benjamin Spector, professor of anatomy at Tufts University School of Medicine and chairman of the Friends of the Armed Forces Medical Library, has been elected president of the American Association of the History of Medicine.

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## NOTICES

### SOUTH END MEDICAL CLUB

The monthly meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, May 15, at 12 noon.

Dr. John Rock will talk on the subject "Management of the Infertile Couple." All physicians are invited to attend.

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### CUTTER LECTURE ON PREVENTIVE MEDICINE

The Harvard School of Public Health announces that Dr. James V. Neel, geneticist, Institute of Human Biology, and associate professor of medical genetics, University of Michigan Medical School, will deliver the Cutter Lecture on Preventive Medicine in the amphitheater of Building D, Harvard Medical School, 25 Shattuck Street, Boston, on Tuesday, May 8, at 5 p.m. Dr. Neel has chosen as his subject, "Human Hemoglobin Types: Their epidemiologic implications."

The medical profession, medical and public-health students and others interested are cordially invited to attend.

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### BOSTON UNIVERSITY SCHOOL OF MEDICINE ALPHA OMEGA ALPHA

The annual spring lecture of the Boston University School of Medicine chapter of Alpha Omega Alpha will be given in the auditorium of the School of Medicine, 80 Concord Street, on Wednesday, May 9, at 5 p.m.

Dr. Francis J. Braceland, president of the American Psychiatric Association, will talk on the subject "Psychiatry in Medical Education."

### JEWISH MEMORIAL HOSPITAL

A medical-staff meeting of the Jewish Memorial Hospital will be held at the hospital, on Monday, April 30, at 8 p.m.

Dr. William Dameshek will talk on the subject "Black and Blue Spots."

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## SOCIETY MEETINGS AND CONFERENCES

April 26 and 27. Lectures on Radiobiology. Page 726, issue of April 12.

April 29–May 3. American Association of Orthodontics. Page 774, issue of April 19.

April 30. Jewish Memorial Hospital. Notice above.

May 1–5. Sixth National Congress on Pediatrics. Page 491, issue of March 8.

May 2. Postgraduate Medical Institute. Page 487, issue of September 15.

May 2–29. Consultation Clinics for Crippled Children in Massachusetts. Page 819.

May 3–5. American Association for Cleft Palate Rehabilitation. Page 774, issue of April 19.

May 3–5. American Goiter Association. Page 348, issue of August 25.

May 8. Cutter Lecture on Preventive Medicine. Notice above.

May 8. Harvard Medical Society. Page 773, issue of April 19.

May 9. Boston University School of Medicine. Alpha Omega Alpha. Notice above.

May 14–17. Armed Forces Institute of Pathology. Page 774, issue of April 19.

May 14–18. American Nurses' Association. Page 491, issue of March 8.

May 15. South End Medical Club. Notice above.

May 16–18. American College of Cardiology. Page 773, issue of April 19.

May 22–24. Massachusetts Medical Society Annual Meeting.

May 23. Boston Branch, American Medical Women's Association. Page 773, issue of April 19.

May 28–June 1. European Symposium on Vitamin B. Page 578, issue of September 29.

June 1–9. International Medical-Surgical Meetings. Page 540, issue of March 15.

June 4–13. Army Medical Service Postgraduate Course. Page 84, issue of July 14.

June 21–23. Society of Nuclear Medicine. Page 1092, issue of December 15.

June 21–24. American Academy of Dental Medicine. Page 944, issue of December 1.

August 19–23. American College of Chest Physicians. Page 840, issue of November 10.

September 3–5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.

September 10–14. American Dietetic Association. Page 1180, issue of December 29.

### CALENDAR FOR THE WEEK BEGINNING THURSDAY, MAY 3

Thursday, May 3

American Association of Orthodontics. Hotel Statler, Boston.

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.

*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.

*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.

*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.

*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.

*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.

*12:00 m.–1:00 p.m. Staff Conference. Stearns Auditorium, New England Center Hospital.

*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.

*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.

*3:00 p.m. Thoracic Conference. Hiatus Hernia — Stricture and Diverticula. Drs. Hugh E. Wilson and Dwight E. Harken. Main Amphitheater, Peter Bent Brigham Hospital.

*7:00 p.m. Boston City Hospital House Officers' Association. Clinical and Experimental Observations of Host-Parasite Relations in Viral Infection. Dr. Louis Weinstein. New Chevver Amphitheater, Dowling Building, Boston City Hospital.

Friday, May 4

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.

*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.

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